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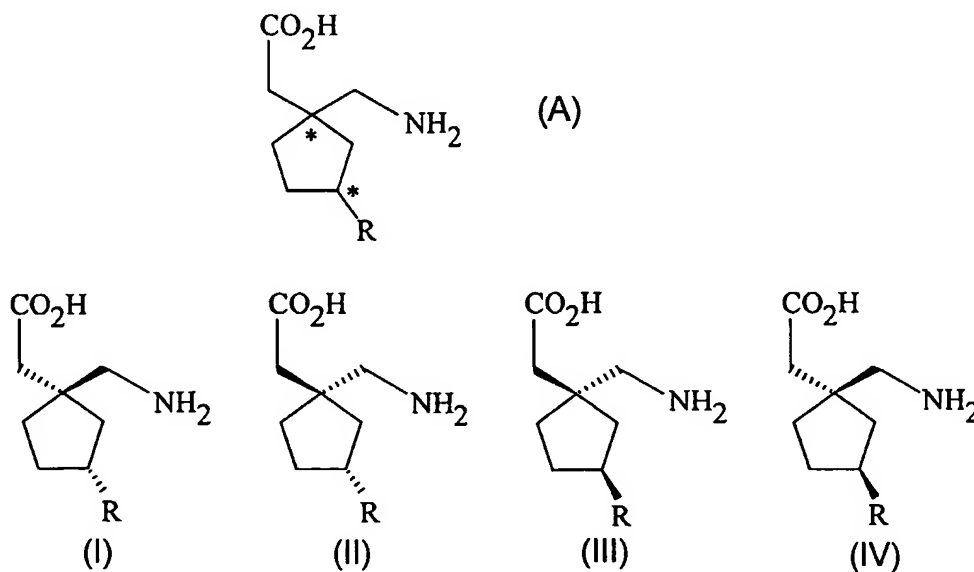
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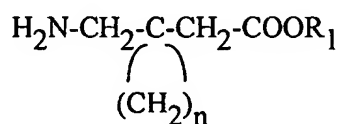
(57) Abstract: The instant invention is a route to stereospecific 3-substituted 5-membered ring isomers of Formula (A). The final products are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammation especially arthritis, sleep disorders, premenstrual syndrome, and hot flashes. The invention provides novel routes to synthesize stereoselectively analogs of gabapentin (Neurontin[®]) of Formulas (I), (II), (III) and (IV) wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof.

WO 01/42190 A1

METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF CYCLIC AMINO ACIDS

BACKGROUND OF THE INVENTION

Compounds of formula

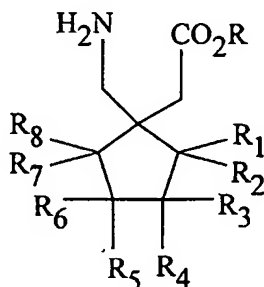


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wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

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United States Serial Number 09/485,382 filed February 8, 2000 teaches in part compounds of Formula I



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I

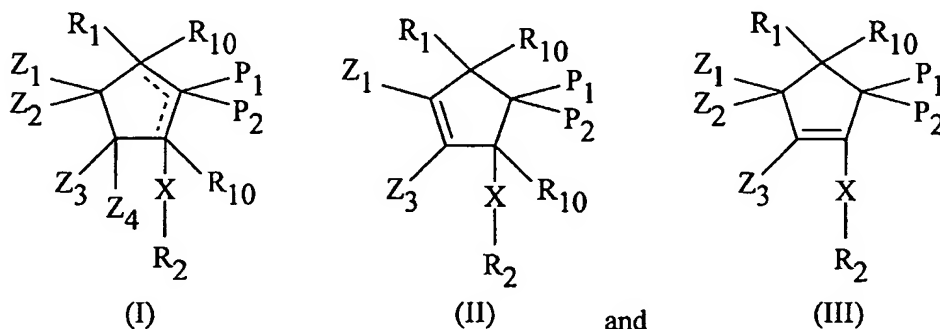
or a pharmaceutically acceptable salt thereof wherein R is hydrogen or a lower alkyl; and R_1 to R_8 are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}_{15}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{R}_{15}$, $-\text{OR}_{15}$ wherein R_{15} is a straight or branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R_1 to R_8 are not

20

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simultaneously hydrogen. This patent application is hereby incorporated by reference.

United States Patent Number 5,929,116 describes endothelin antagonists of formulas



wherein

R_1 is $-X(CH_2)_nAr$;

R_2 is Ar;

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

R_3 and R_5 are independently hydrogen, R_{11} , OH, C_{1-8} alkoxy, $S(O)_qR_{11}$,

$N(R_6)_2$, Br, F, I, Cl, CF_3 , $NHCO R_6$, $-R_{11}CO_2R_7$, $-XR_9-Y$, or

$-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11} , OH, C_{1-5} alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, $-X(R_{11})$, Br, F, I, Cl, or $NHCO R_6$ wherein the C_{1-5} alkoxy may be unsubstituted or substituted by OH, methoxy, or halogen;

R_6 is independently hydrogen or C_{1-4} alkyl;

R_7 is independently hydrogen, C_{1-6} alkyl, or $(CH_2)_nAr$;

R_8 is hydrogen, R_{11} , CO_2R_7 , PO_3H_2 , $SO_2NR_7R_{11}$, $NR_7SO_2R_{11}$, $P(O)(OH)R_7$, CN, $-C(O)N(R_6)_2$, tetrazole, or OR_6 ;

R_9 is C_{1-10} alkyl, C_{2-10} alkenyl, or phenyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, $COOH$, $>C=O$, halogen, or XC_{1-5} alkyl;

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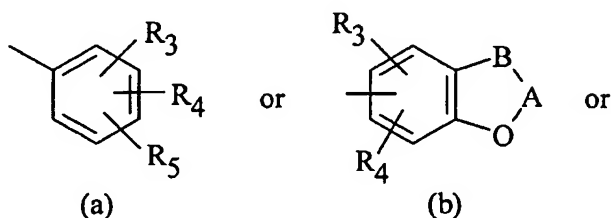
R_{10} is R_3 or R_4 ;

R_{11} is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, all of which may be unsubstituted or substituted by one or more OH, CH_2OH , $N(R_6)_2$, or halogen;

X is $(CH_2)_n$, O, NR_6 , or $S(O)_q$;

5 Y is CH_3 or $X(CH_2)_nAr$;

Ar is:



naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is $>C=O$, or $[C(R_6)_2]_m$;

B is $-CH_2-$ or $-O-$;

15 Z_1 , Z_2 , Z_3 , and Z_4 are independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, OH, C_{1-8} alkoxy, $S(O)_qC_{1-8}$ alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$, $-X(CH_2)_nR_8$, XR_9Y , phenyl, benzyl, or C_{3-6} cycloalkyl wherein the C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl may be optionally substituted by $COOH$, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen;

q is zero, one, or two;

n is an integer from 0 to 6;

m is 1, 2, or 3;

and the dotted line in Formula (I) indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

- when the optional double bond is present, there is only one R_{10} , there is no P_1 , and P_2 is not NR_6R_9Y ;

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- X is not NR_6 , and Z_3 is not OH or $\text{N}(\text{R}_6)_2$ in Formula (III);
- Z_1 and Z_3 are not OH, $\text{N}(\text{R}_6)_2$, or Iodine in Formula (II);
- when the optional double bond is present in Formula (I) and X-R_2 is attached to the double bond, X is not NR_6 ;
- 5 • when the optional double bond is present in Formula (I) and R_1 is attached directly to the double bond, R_1 is not NR_6Ar ;
- when R_3 , R_5 , Z_1 , Z_2 , or Z_3 is $\text{X}(\text{CH}_2)_n\text{R}_8$ and n is not zero, X is oxygen or NR_6 when R_8 is OR_6 or CO_2H .

10 Also included in the invention are pharmaceutically acceptable salts of the active compounds.

Most or all of the desired pharmacological activity of a compound comprised of two or more stereoisomers frequently resides in just one of the stereoisomers. The other stereoisomer(s) typically is inactive at best or exhibits undesirable side effects such as, for example, toxicity. Therefore where a
15 compound is comprised of two or more stereoisomers, it is important, and sometimes mandatory, to develop a method of selectively preparing the beneficial stereoisomer in a form that is free from, or almost free from, contamination by the other inactive or harmful stereoisomer(s). However, usually it is very difficult to discover a method for the preparation of a beneficial stereoisomer in a form that is
20 free from, or almost free from, contamination by the other inactive or harmful stereoisomer(s). Unexpectedly, we have invented novel preparations of certain important 3-substituted cyclopentyl-containing, amino acid analogs of gabapentin, a marketed anticonvulsant, which provide the desirable stereoisomers with a high degree of stereochemical purity.

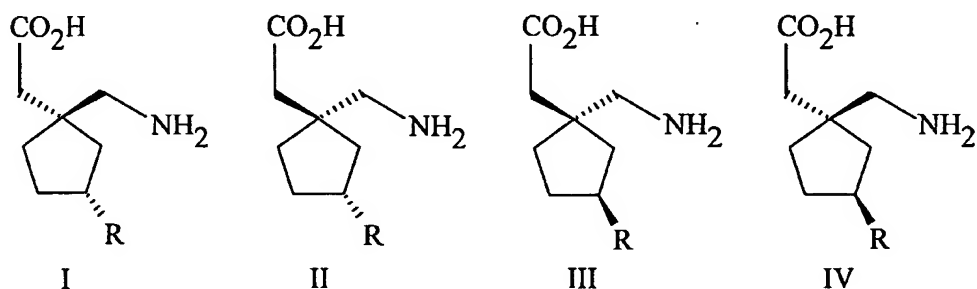
25 None of the above teach the synthesis of the instant invention.

SUMMARY OF THE INVENTION

The instant invention encompasses novel synthetic routes for the preparation of important 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof. Gabapentin, marketed under the

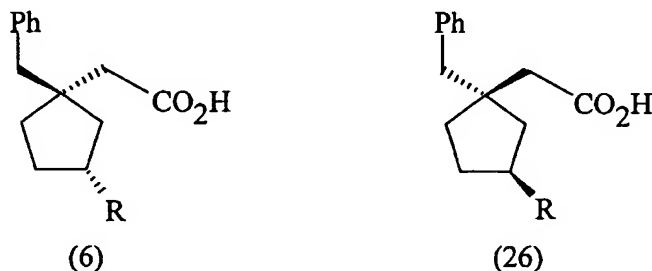
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trade name Neurontin® for the treatment of seizure disorders, particularly epilepsy, provides well-known medical benefits to patients in need of such treatment. The instant invention encompasses novel synthetic routes for the preparation of 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof that enable the synthesis of each stereoisomer of these analogs with a high degree of stereochemical purity. These routes provide access to pure stereoisomers of Formulas I, II, III, and IV



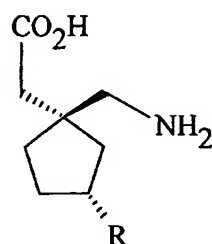
wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl.

Further, the invention encompasses the key intermediates of formulas (6) and (26). Still further, the invention provides novel synthetic routes for the preparation of compounds of formulas (6) and (26). The routes enable the synthesis of each stereoisomer of compounds of formulas (6) and (26) with a high degree of stereochemical purity. These routes provide access to pure stereoisomers of formulas (6) and (26) wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl.



The invention provides a process for the preparation of a compound of Formula I

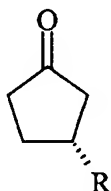
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I

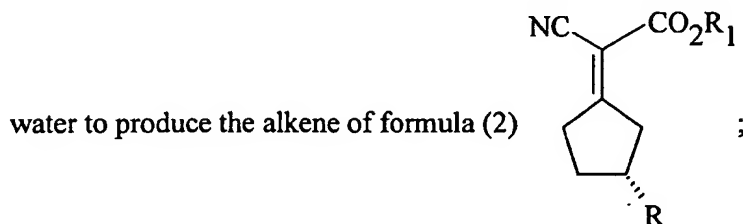
wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)

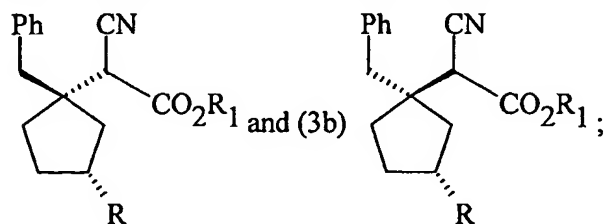


, a solvent, a carboxylic acid, and a Knoevenagel reaction

catalyst, and stirring the mixture in the presence of a means of removing

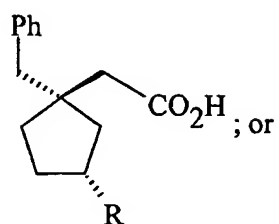
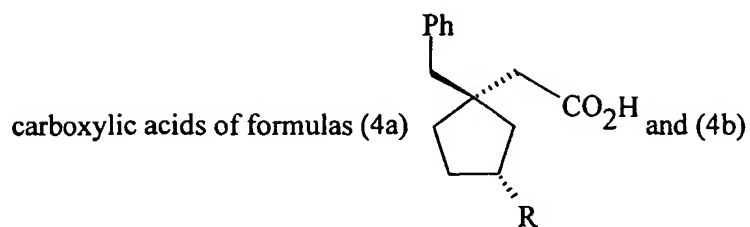


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)

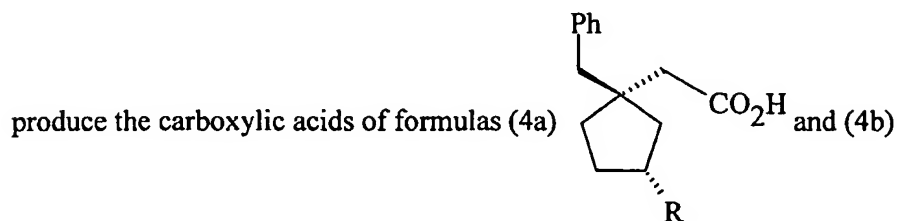


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent and stirring, and then acidifying to produce the

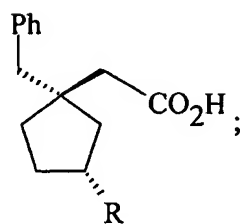
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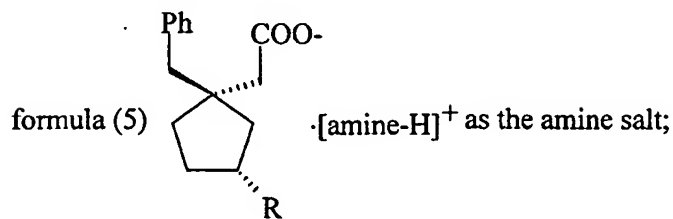
adding the products of Step b) above to an acid mixture and stirring to



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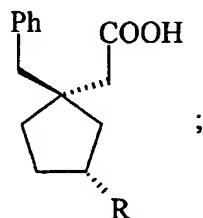


- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



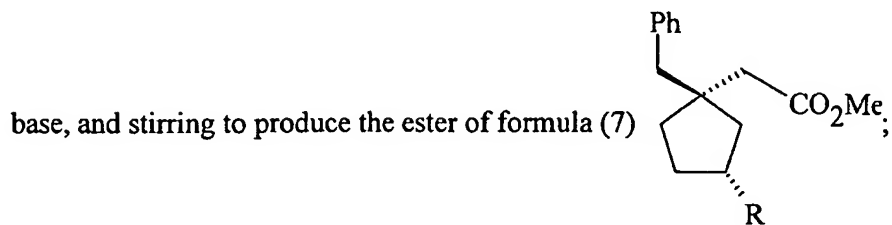
- e) converting the product of Step d) to a carboxylic acid of formula (6)

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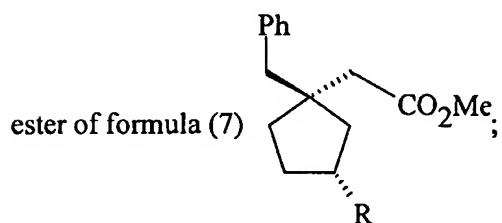


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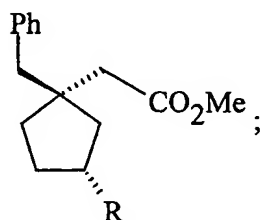
- f) adding the product of Step e) to a mixture of iodomethane, a solvent, and a



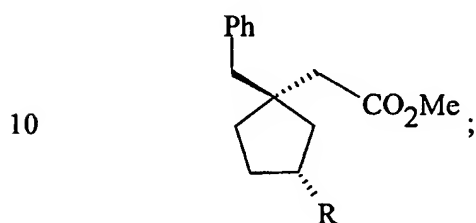
or adding the product of Step e) to methanol and an acid to produce the



- 5 or adding the product of Step e) above to trimethylsilyldiazo-methane and methanol in a solvent to produce the ester of formula (7)



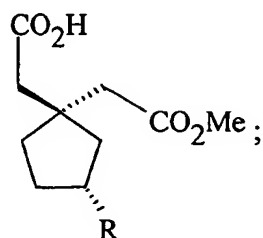
or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in a solvent to produce ester of formula (7)



- g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III)

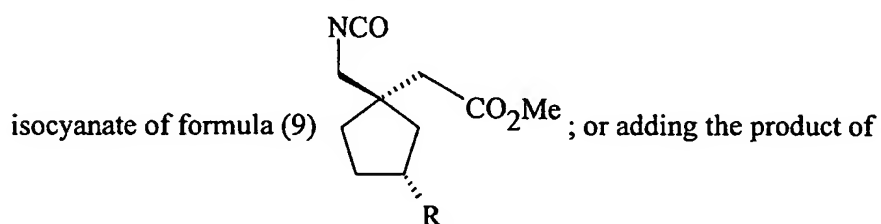
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chloride, and stirring to produce the carboxylic acid of formula (8)



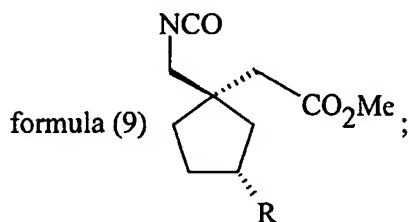
- h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the

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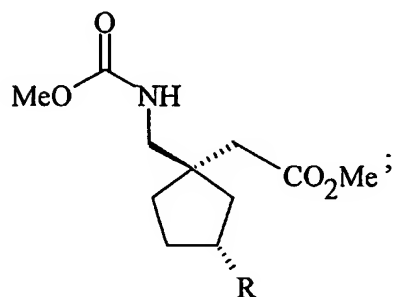


Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of

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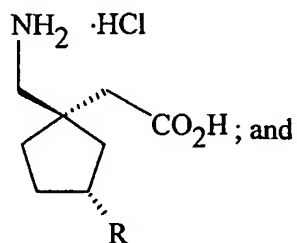


- i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (10)

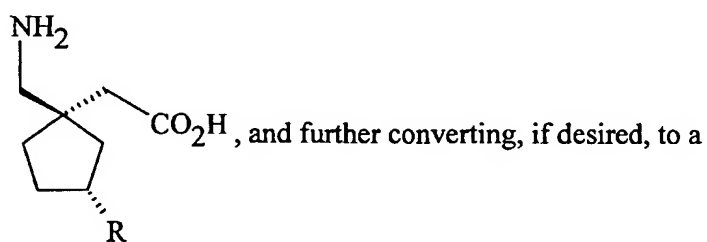


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- j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (Ia)



- k) converting the product of Step j) to a compound of formula (I)



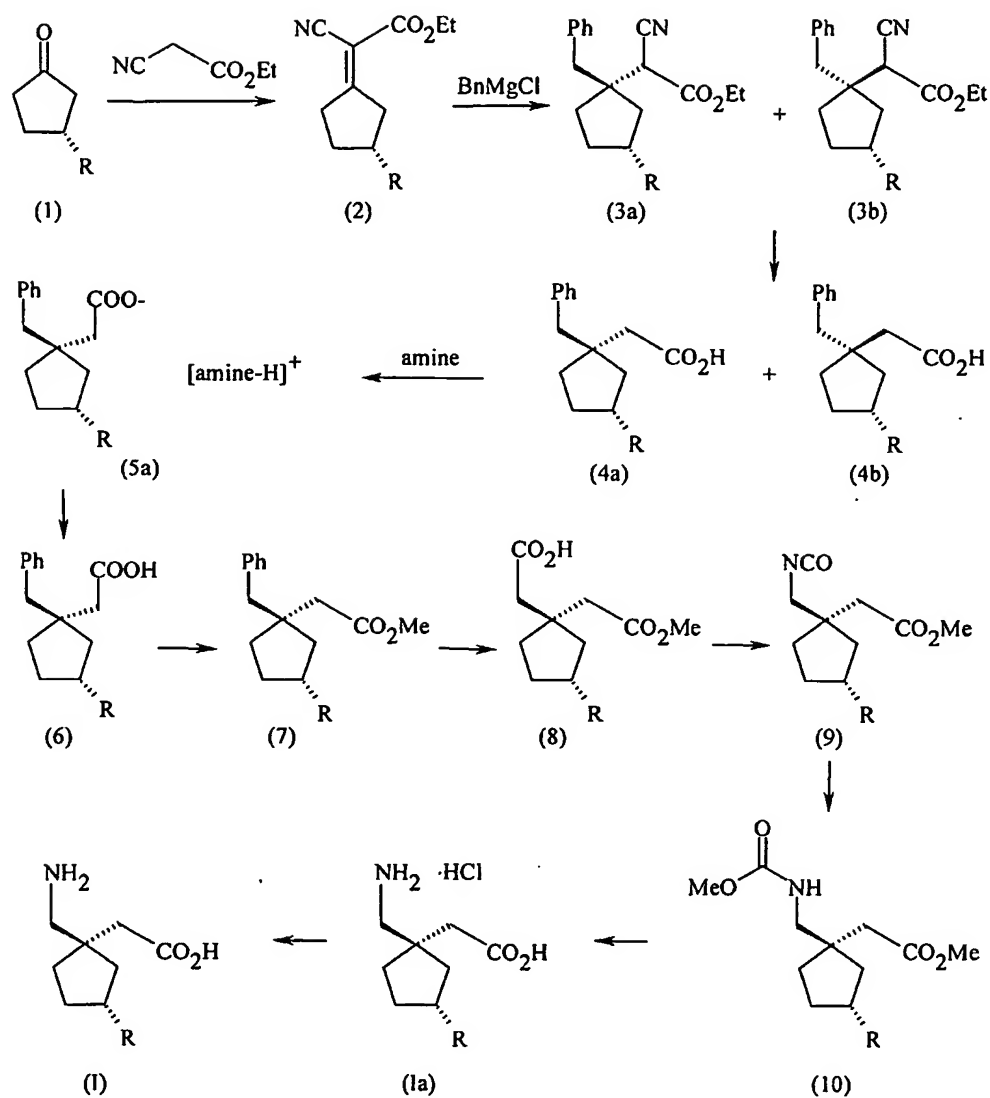
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pharmaceutically acceptable salt by known means.

This process is outlined in Scheme 1.

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Scheme 1

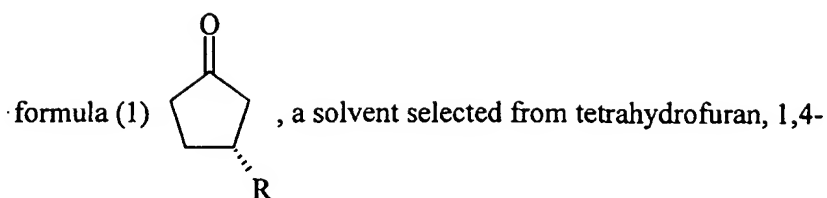


Preferred is a process for the preparation of a compound of Formula I wherein R is C_1 - C_{10} alkyl or C_3 - C_{10} cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

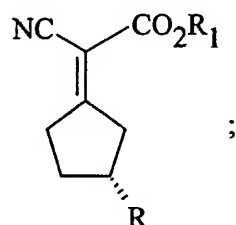
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- adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of

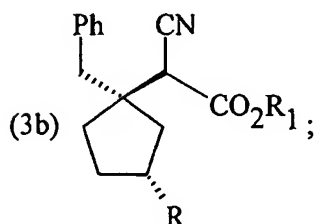
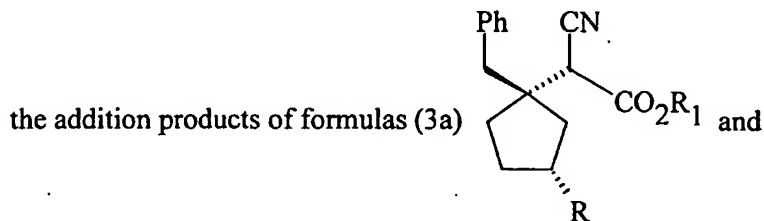
-12-



dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

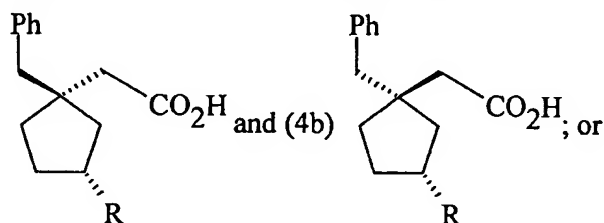


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce

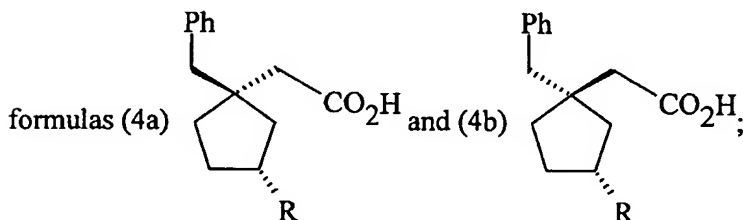


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- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (4a)

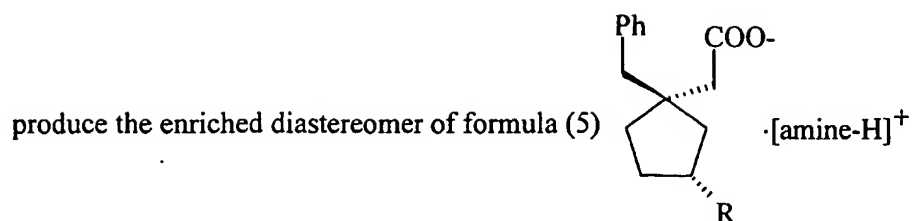


adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of



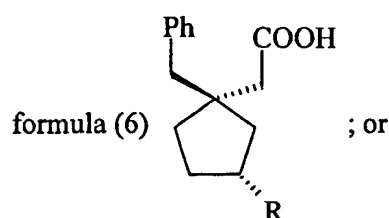
- d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to

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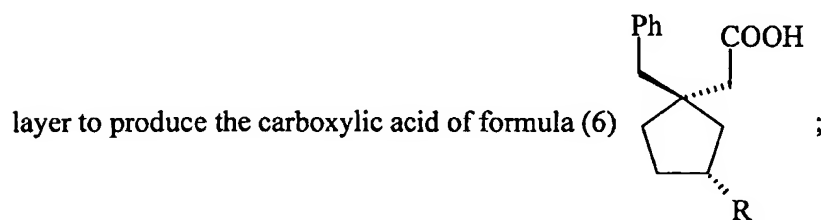


as the amine salt;

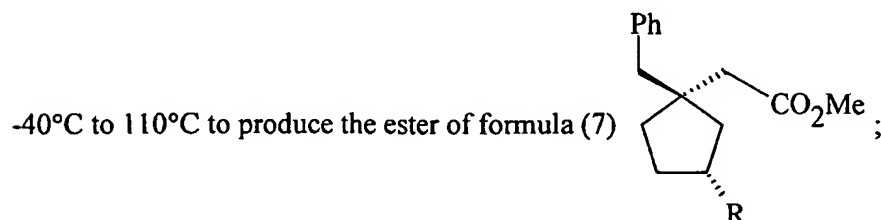
- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water is added and stirring to produce the carboxylic acid of



partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic

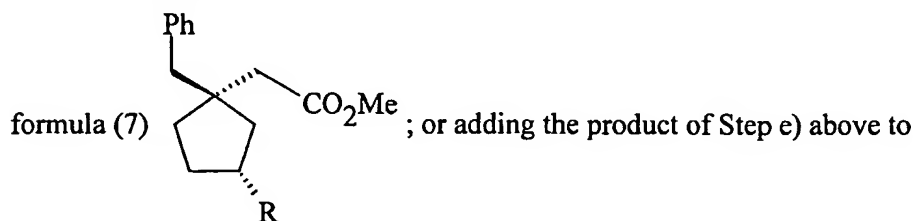


- f) adding the product of Step e) above to a mixture of iodomethane, a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene, and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and stirring at a temperature of from

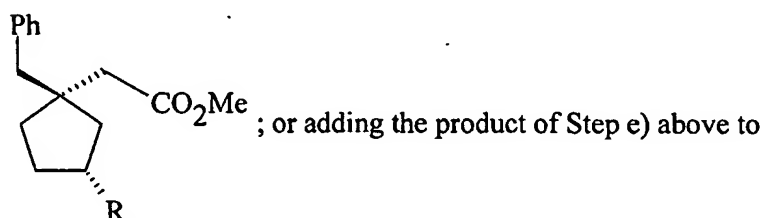


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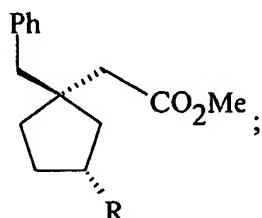
or adding the product of Step e) above to a mixture of methanol and concentrated sulphuric acid, concentrated hydrochloric acid, or hydrogen chloride at a temperature of from 0°C to 100°C to produce the ester of



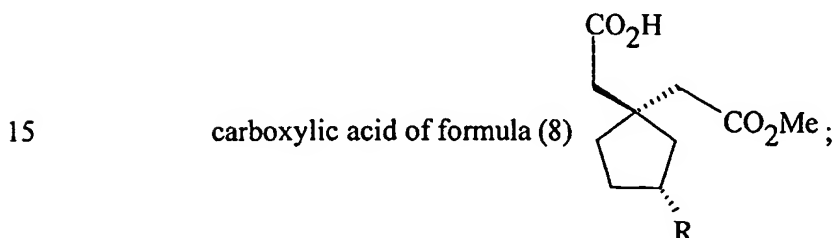
- 5 trimethylsilyldiazomethane and methanol in benzene or toluene at a temperature of from -40°C to 100°C to produce the ester of formula (7)



- 10 diazomethane or trimethylsilyldiazomethane in a solvent selected from benzene, toluene, dichloromethane, and diethyl ether at a temperature of from -40°C to 40°C to give a compound of formula (7)



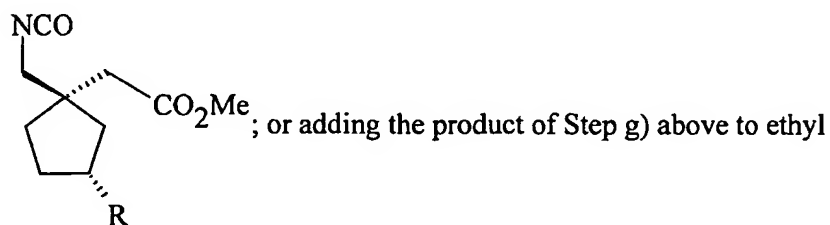
- g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the



- h) adding the product of Step g) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene,

-16-

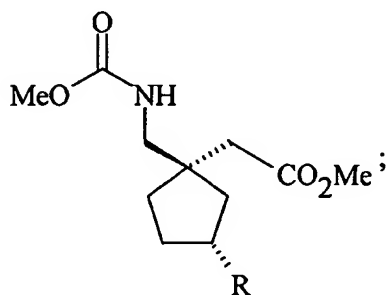
benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from 0°C to 150°C to produce the isocyanate of formula (9)



- 5 chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and

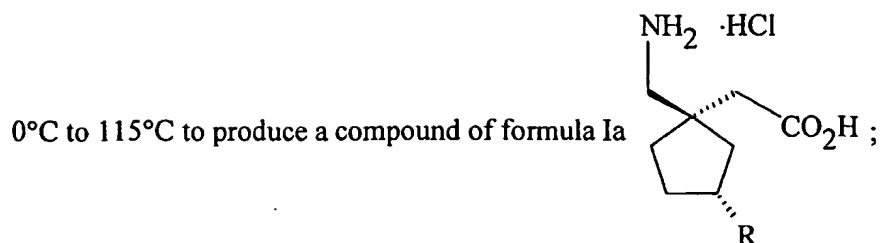
- 10 refluxing to produce the isocyanate of formula (9)
-
- Chemical structure (9) is an isocyanate derivative. It consists of a cyclopentane ring. One carbon of the ring is bonded to an NCO group (isocyanate) via a solid wedge bond. The adjacent carbon is bonded to a CO₂Me group (methyl ester) via a dashed wedge bond. Another carbon on the ring is bonded to an R group via a dashed wedge bond.

- i) adding the product of Step h) to a mixture of a solvent selected from toluene, benzene, xylenes and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (10)



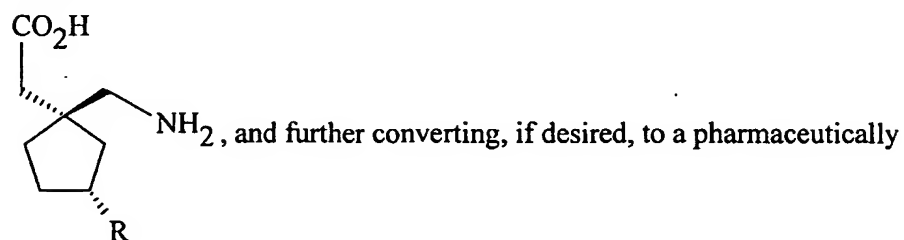
- 15 j) adding the product of Step i) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from

-17-



and

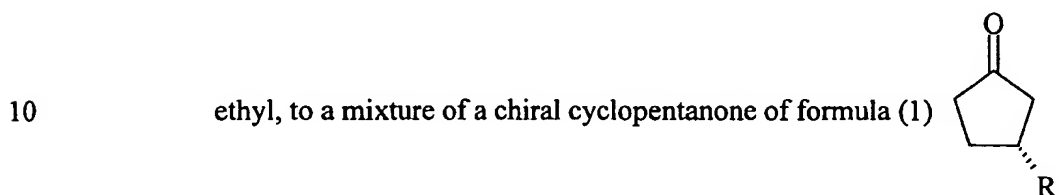
- k) converting the product of Step j) to a compound of Formula I



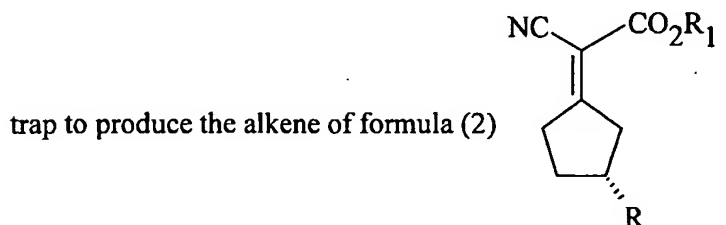
- 5 acceptable salt by known means.

More preferred is a process for the preparation of a compound of Formula I wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) NC-CH₂-CO₂R₁, wherein R₁ is

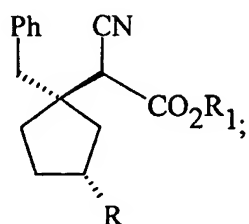
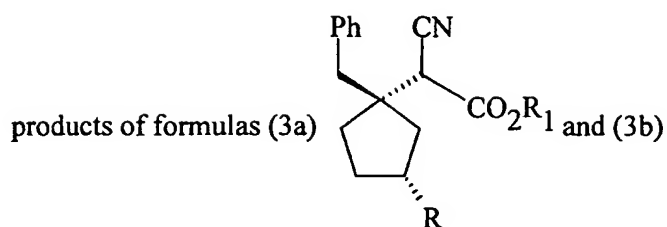


toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark

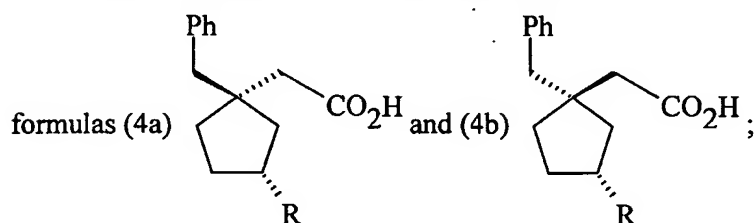


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition
- 15

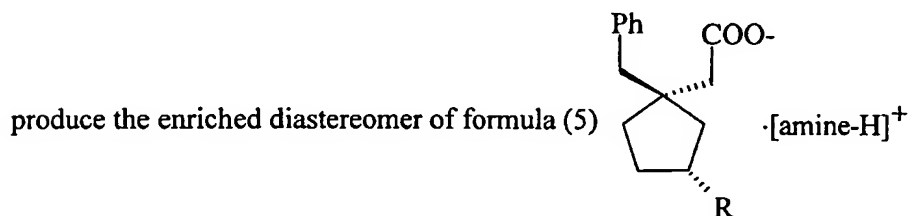
-18-



- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of

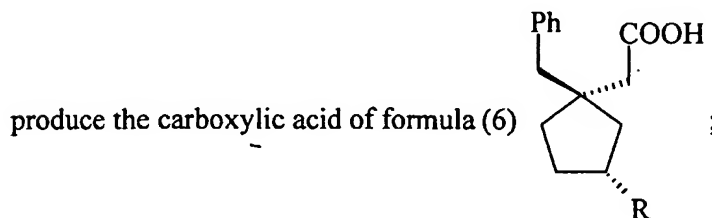


- d) contacting the products of Step c) above with (S)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to



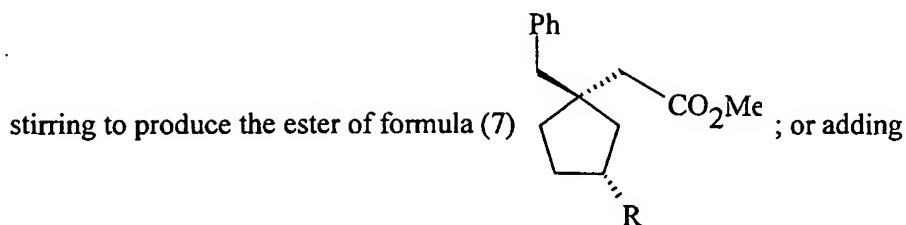
- 10 as the (S)- α -methyl-benzylamine salt;

- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to

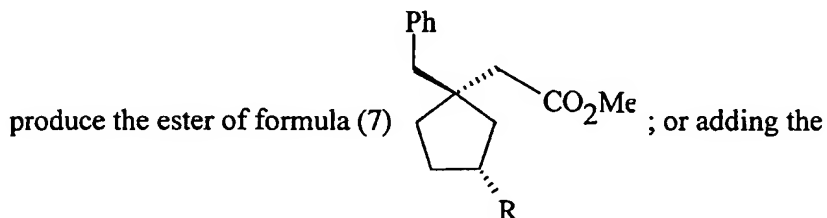


- f) adding the product of Step e) to a mixture of iodomethane, dichloromethane, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and

-19-

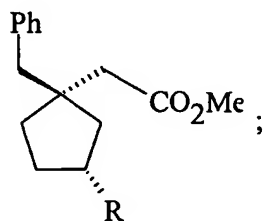


the product of Step e) to methanol and concentrated sulfuric acid to



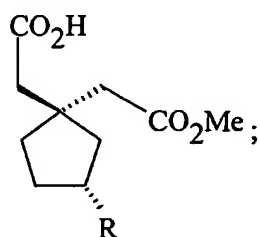
product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in dichloromethane to produce the ester of formula (7)

5

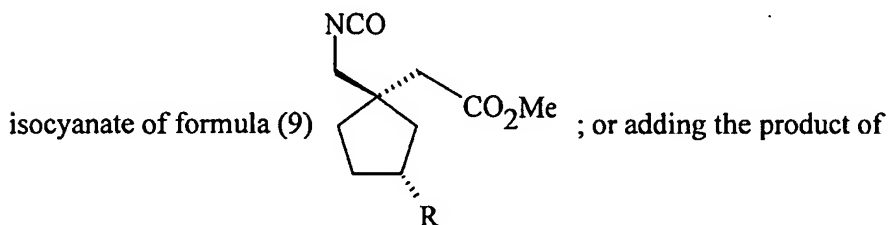


- g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (8)

10



- h) adding the product of Step g) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the

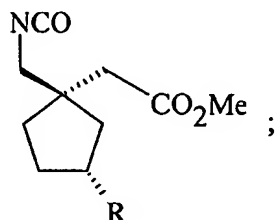


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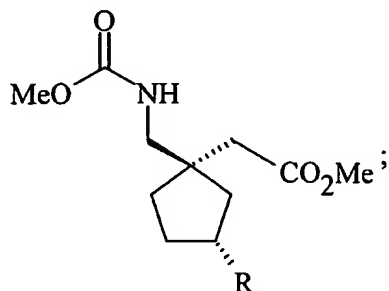
Step g) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran, followed by adding toluene or benzene, and refluxing to

5

produce ester of formula (9)

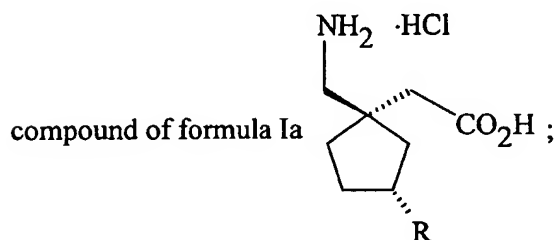


- i) adding the product of Step h) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (10)

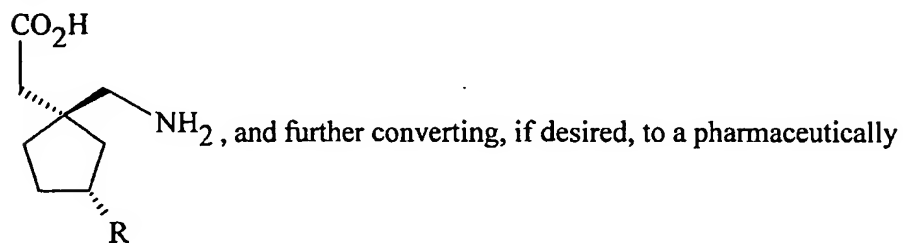


10

- j) adding the product of Step i) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a



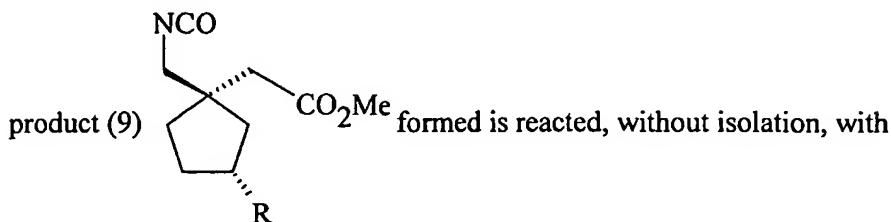
- k) converting the product of Step j) to a compound of Formula I



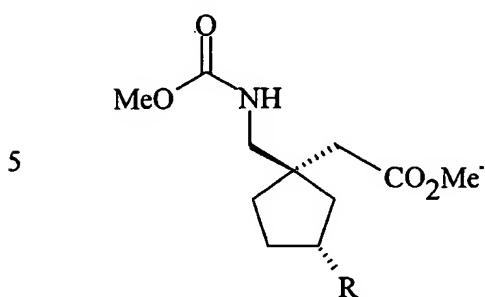
acceptable salt by known means.

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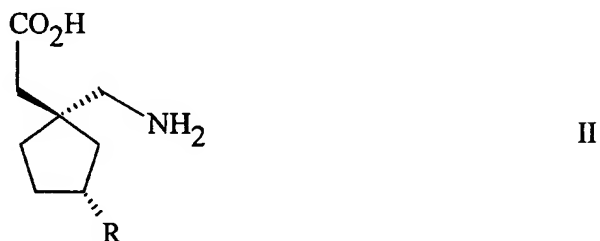
Also preferred is a process for the preparation of a compound of Formula I as described above, further characterized in that the intermediate



methanol to produce the carbamate of formula (10)

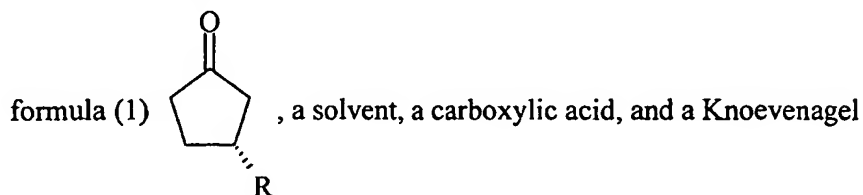


Further, the invention provides a process for the preparation of a compound of Formula II



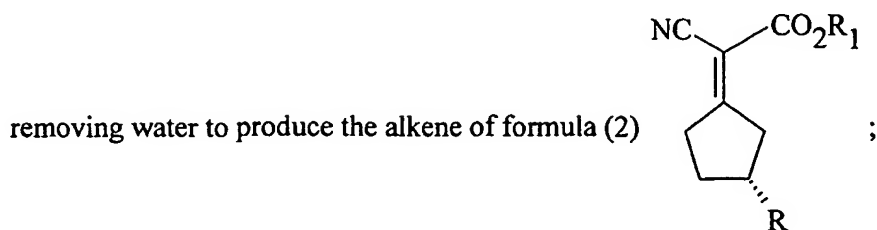
wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- 10 a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

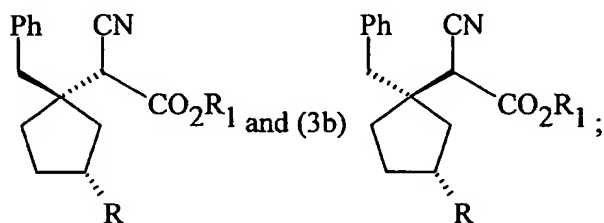


-22-

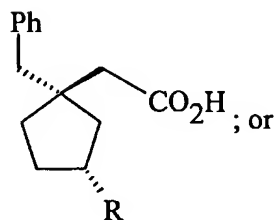
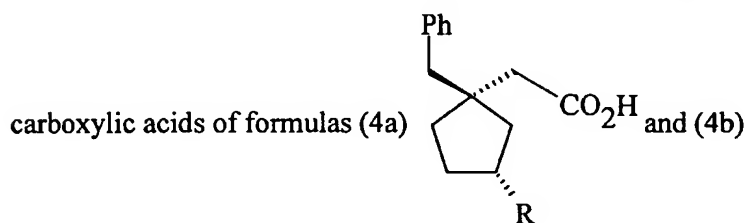
reaction catalyst, and stirring the mixture in the presence of a means of



- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)

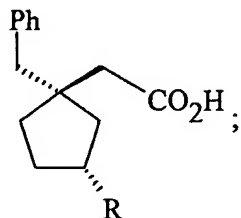
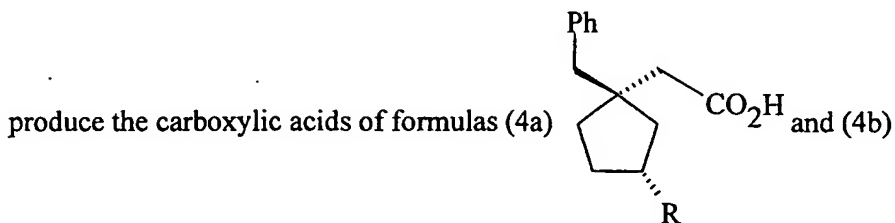


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide and a solvent, and stirring, and then acidifying to produce the

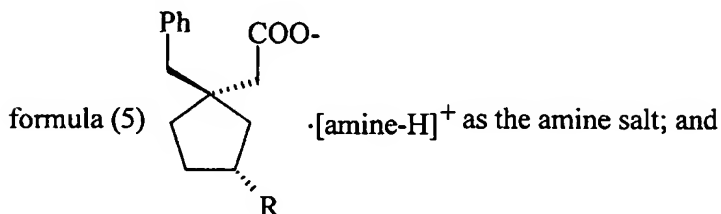


-23-

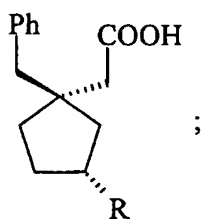
adding the products of Step b) above to an acid mixture and stirring to



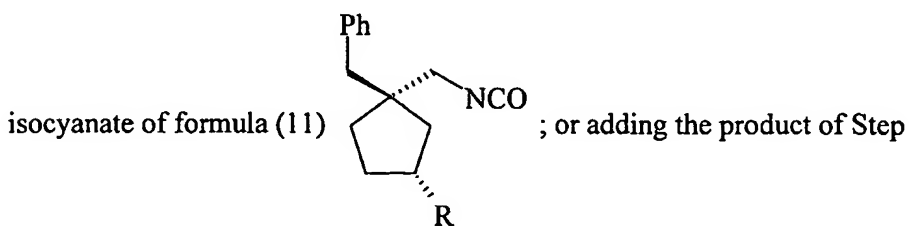
- 5 d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



- e) converting the product of Step d) to a carboxylic acid of formula (6)



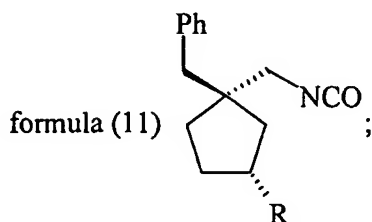
- 10 f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the



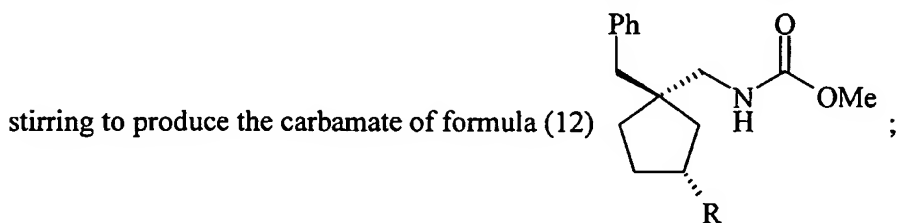
e) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed

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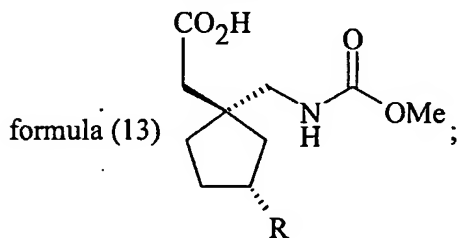
by adding toluene or benzene, and refluxing to produce isocyanate of



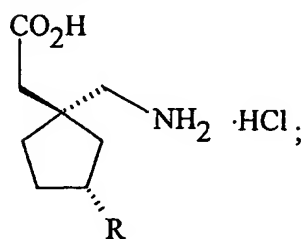
g) adding the product of Step f) to a mixture of a solvent and methanol, and



5 h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

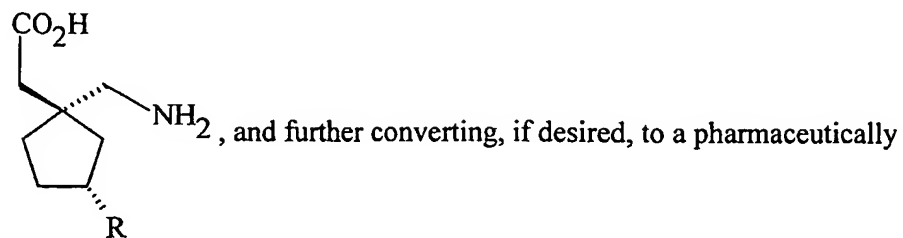


10 i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IIa)



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j) converting the product of Step i) to a compound of formula (II)

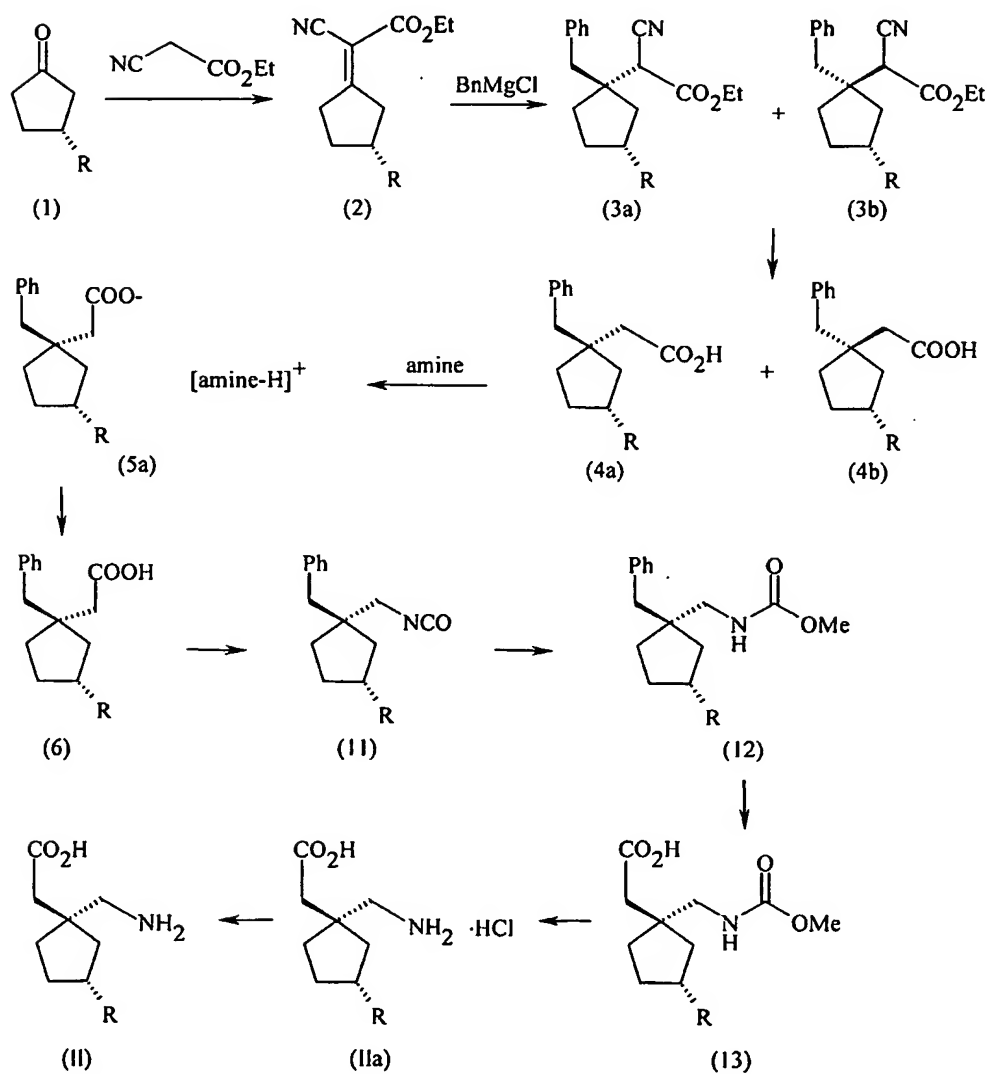


acceptable salt by known means.

This process is outlined below in Scheme 2.

5

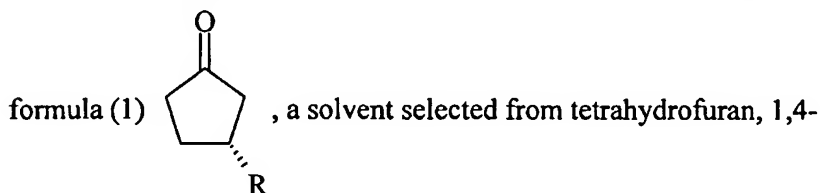
Scheme 2



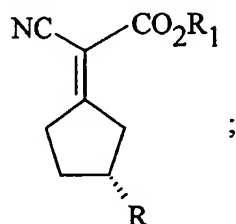
-26-

Preferred is a process for the preparation of a compound of Formula II wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$ wherein R₁ is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of

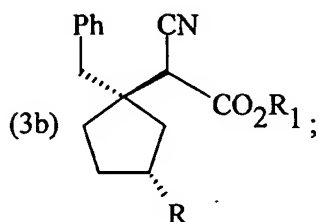
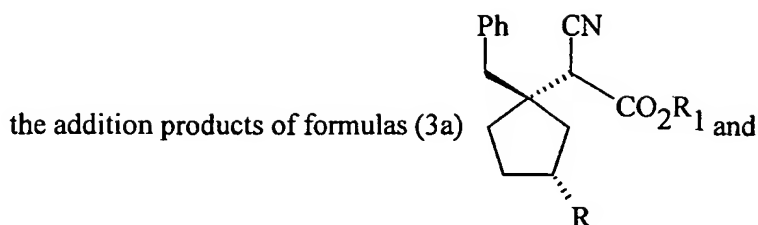


dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β-alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

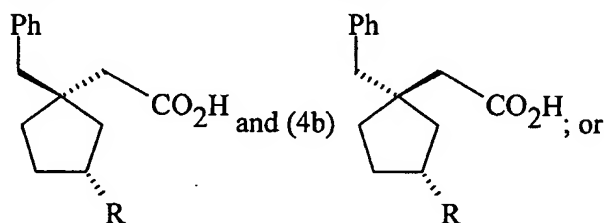


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce

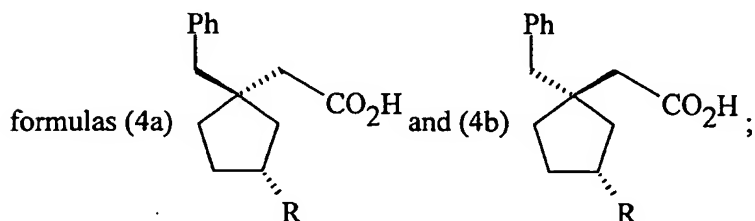
-27-



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic acids of formulas (4a)



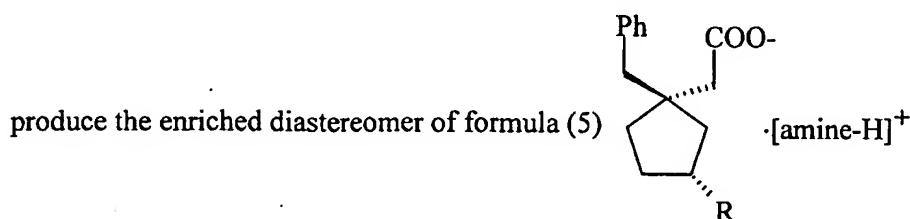
adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of



- d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and

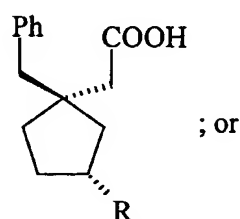
-28-

pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to

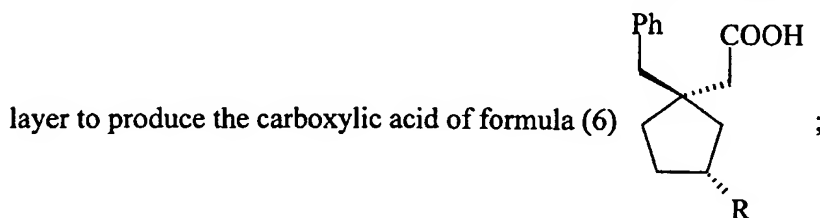


as the amine salt;

- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)

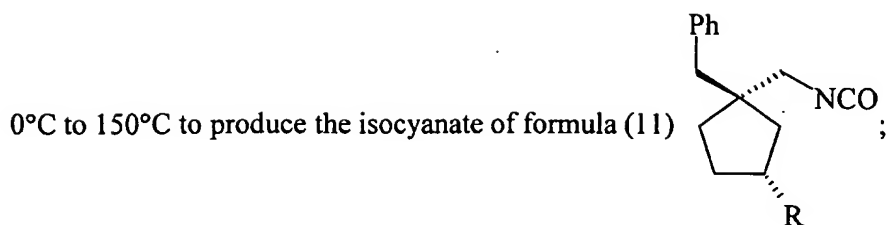


partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic

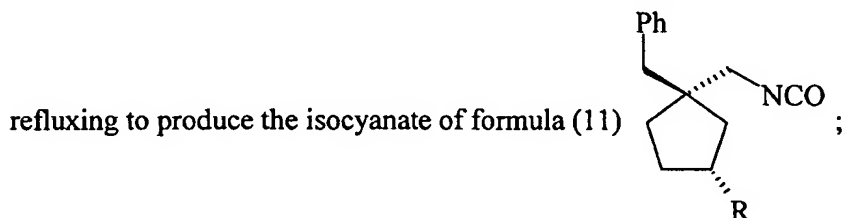


- f) adding the product of Step e) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from

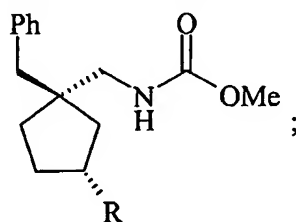
-29-



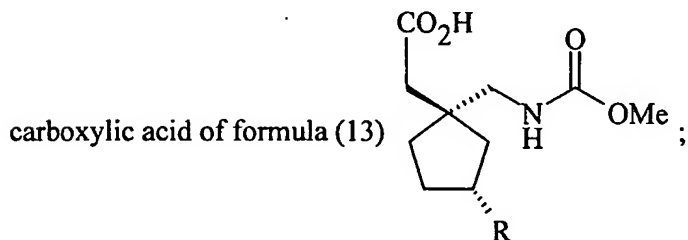
or adding the product of Step e) above to ethyl chloroformate or isobutyl chloroformate and a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and



- g) adding the product of Step f) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (12)

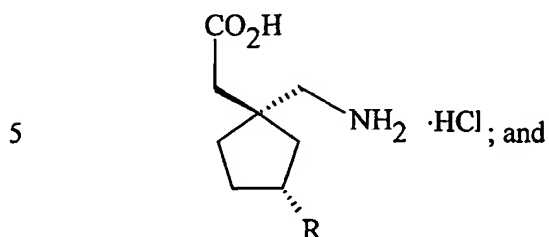


- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the

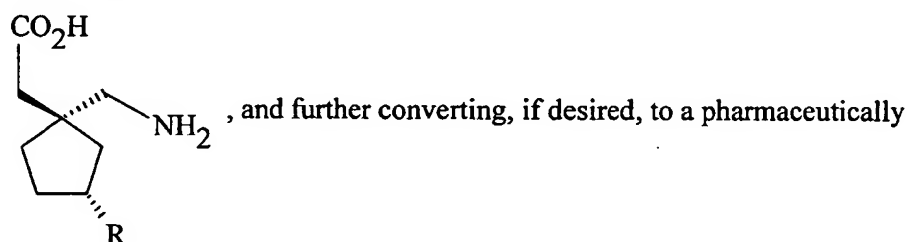


-30-

- i) adding the product of Step h) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa



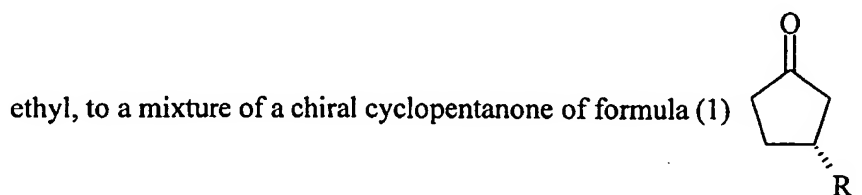
- j) converting the product of Step i) to a compound of Formula II



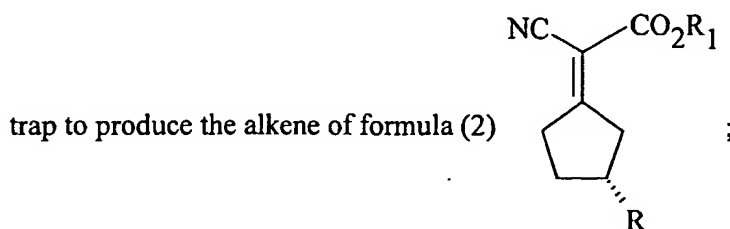
acceptable salt by known means.

10 More preferred is a process for the preparation of a compound of Formula II wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is

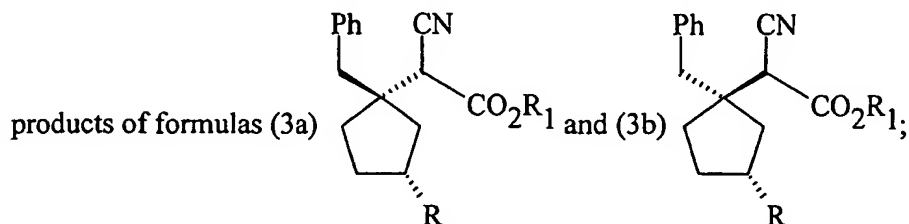


15 toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark

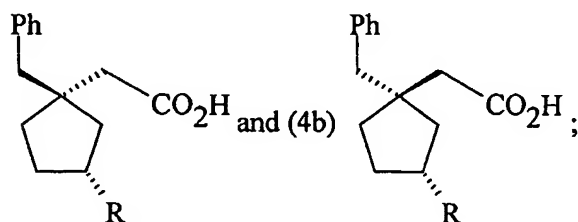


-31-

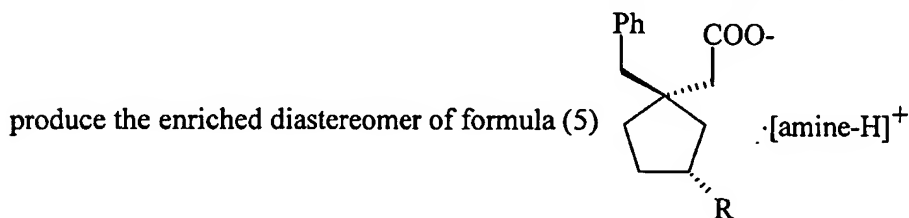
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition



- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C , and then acidifying to produce the hydrolysis products of formulas (4a)

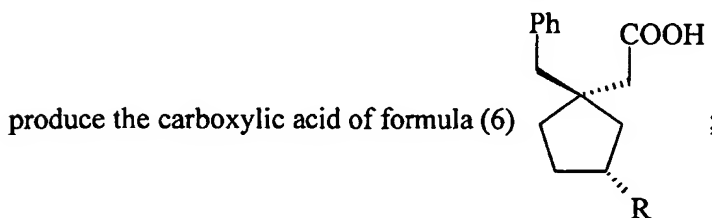


- d) contacting the products of Step c) above with (S)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to



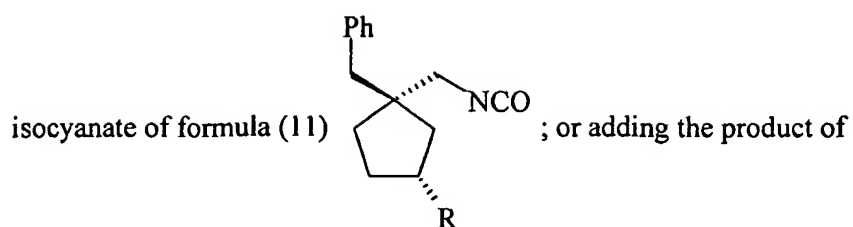
as the (S)- α -methyl-benzylamine salt;

- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to

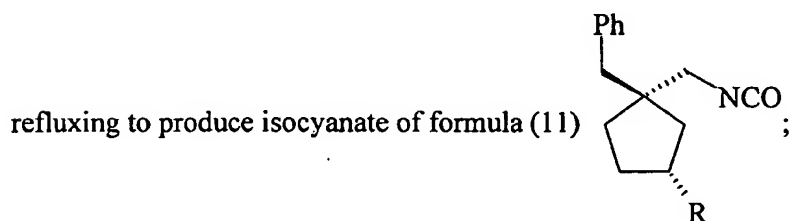


- f) adding the product of Step e) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the

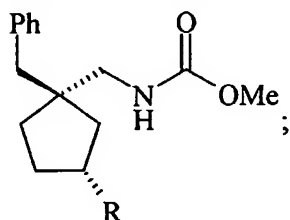
-32-



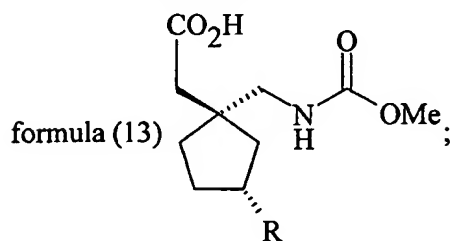
Step e) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and



- g) adding the product of Step f) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (12)

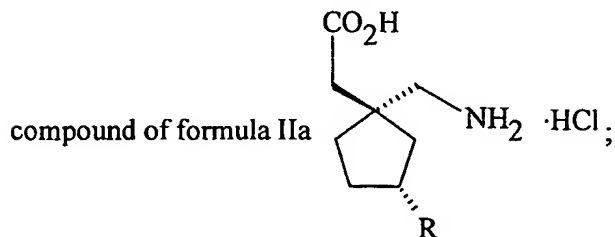


- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

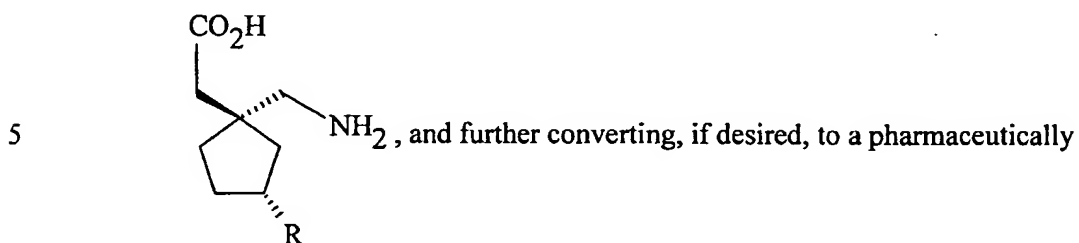


-33-

- i) adding the product of Step h) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a

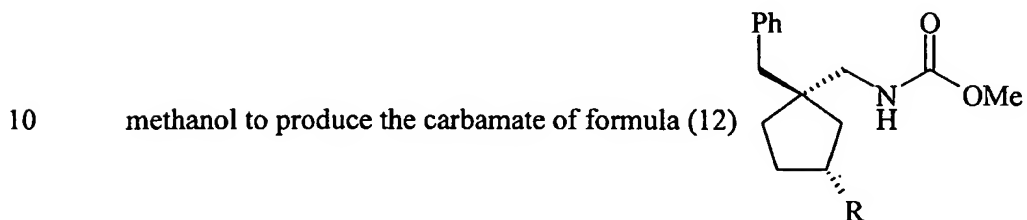
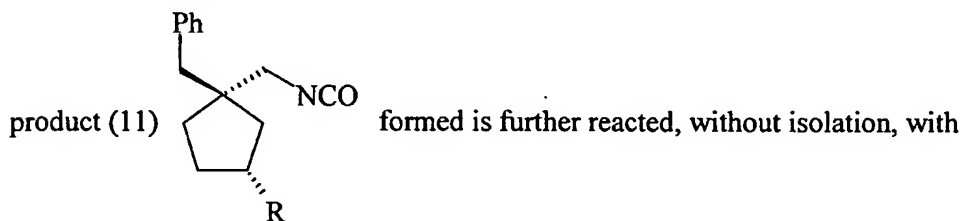


- j) converting the product of Step i) to a compound of Formula II



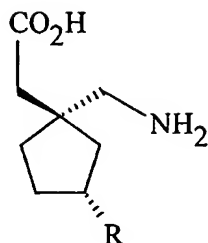
acceptable salt by known means.

Also preferred is a process for the preparation of a compound of Formula II as described above, further characterized in that the intermediate



Still further, the invention provides a process for the preparation of a compound of Formula II

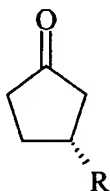
-34-



II

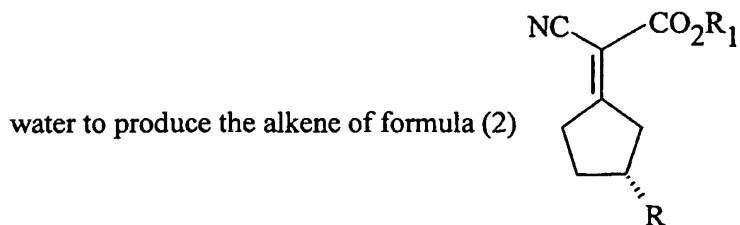
wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)

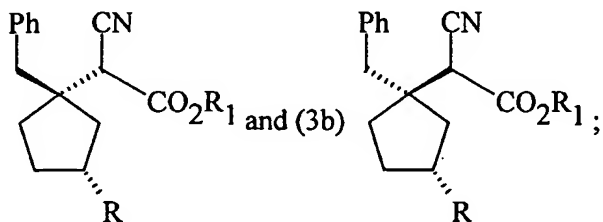


, a solvent, a carboxylic acid, and a Knoevenagel reaction

catalyst, and stirring the mixture in the presence of a means of removing

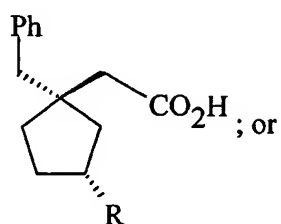
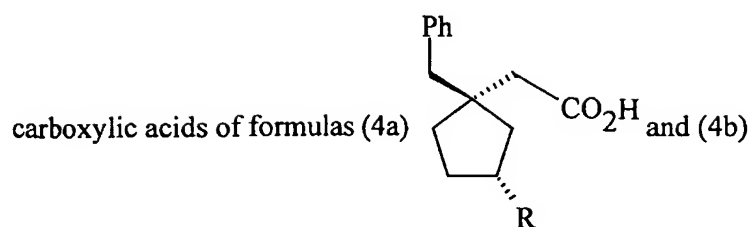


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)

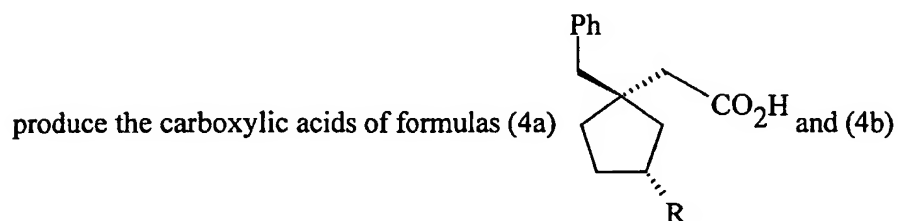


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

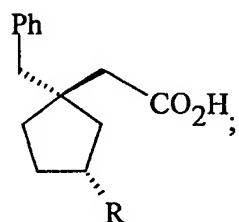
-35-



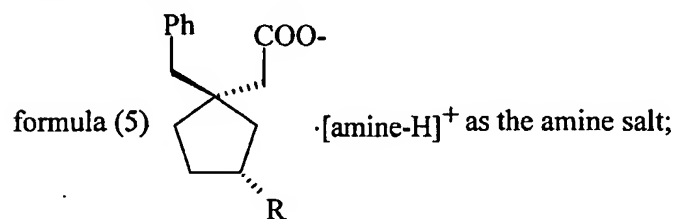
adding the products of Step b) above to an acid mixture and stirring to



5

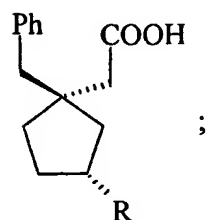


- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



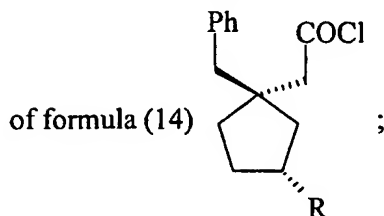
- e) converting the product of Step d) to a carboxylic acid of formula (6)

10

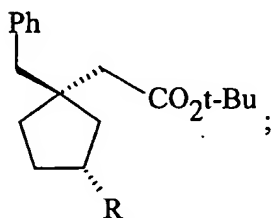


-36-

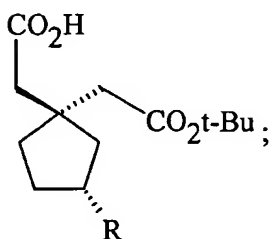
- f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce the acid chloride



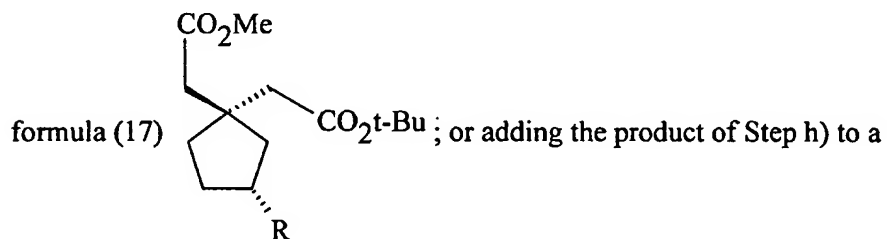
- g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of formula (15)



- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (16)

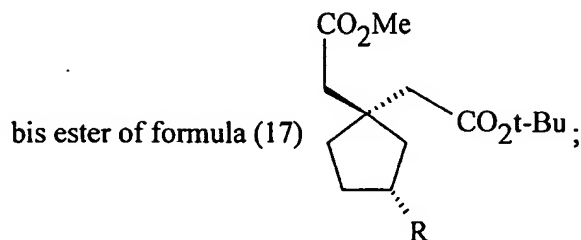


- i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of

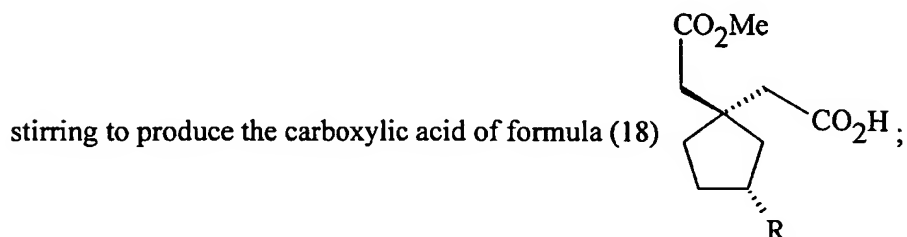


-37-

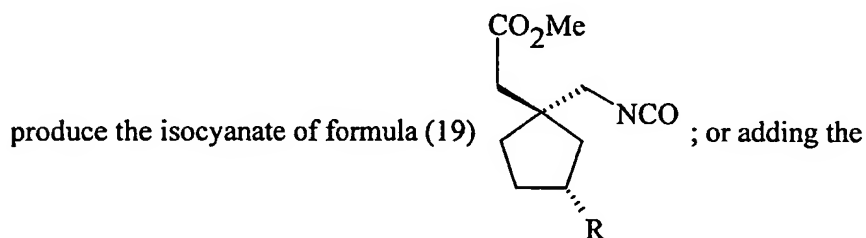
mixture of iodomethane, a solvent, and a base, and stirring to produce the



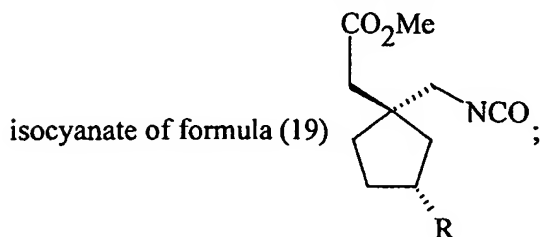
j) adding an acid to a mixture of the product from Step i) and a solvent, and



5 k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring to

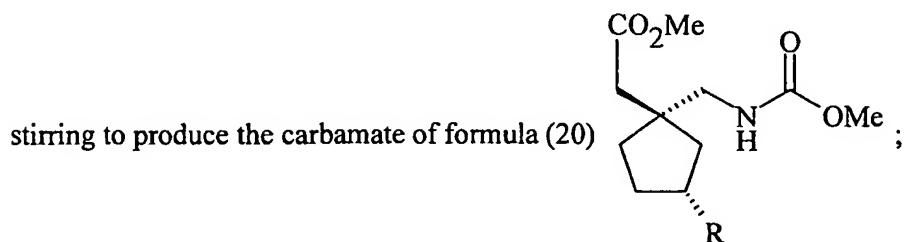


product of Step j) above to ethyl chloroformate or isobutyl chloroformate
and a base in a solvent at a temperature of from -40°C to 78°C, followed
by adding a solution of sodium azide in water and tetrahydrofuran or
10 acetone, followed by adding toluene or benzene, and refluxing to produce

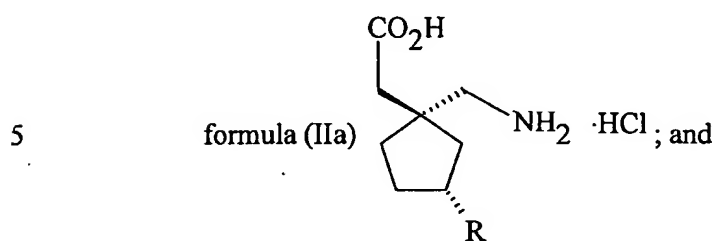


-38-

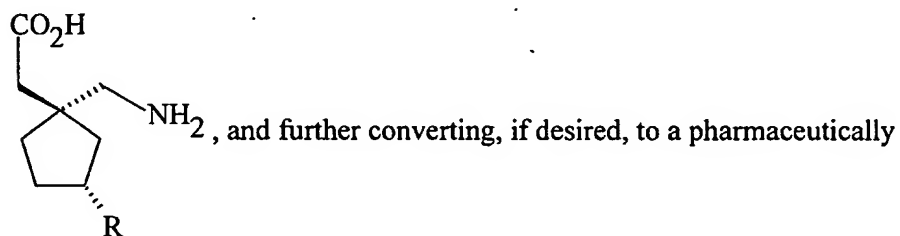
- l) adding the product of Step k) to a mixture of a solvent and methanol, and



- m) adding the product of Step l) to a mixture of a solvent and aqueous hydrochloric acid is added, and stirring to produce a compound of



- n) converting the product of Step m) to a compound of formula (II)

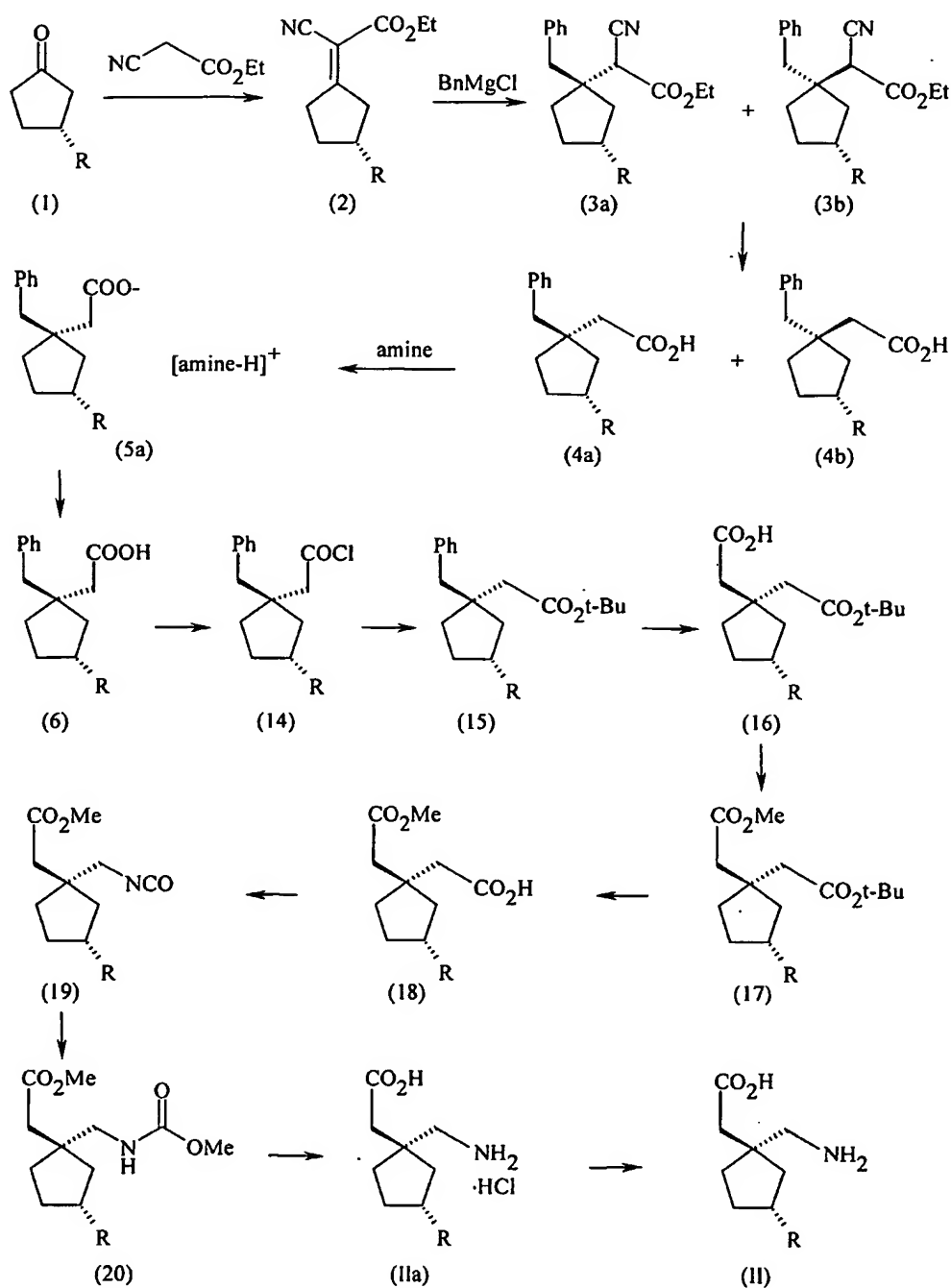


acceptable salt by known means.

This process is outlined in Scheme 3.

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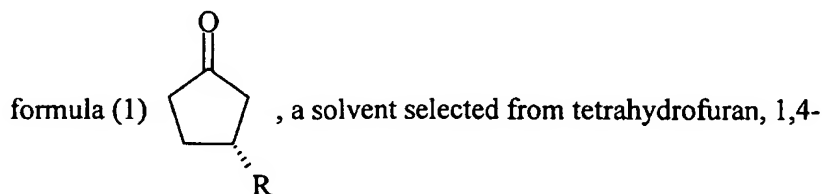
Scheme 3



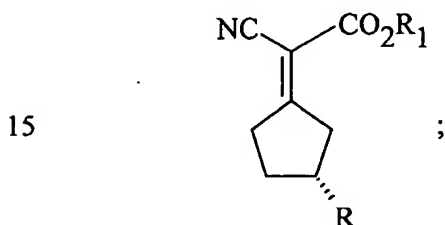
Preferred is a process for the preparation of a compound of Formula II wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

-40-

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of

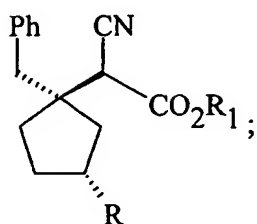
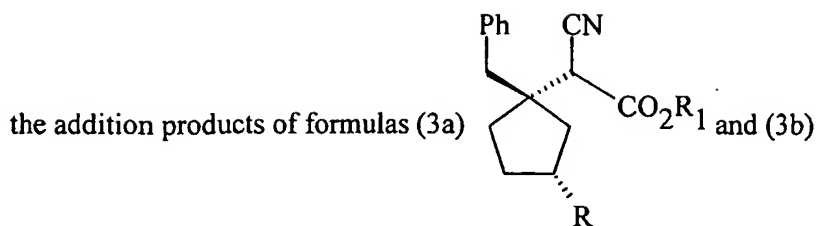


- 5 dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in
- 10 the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

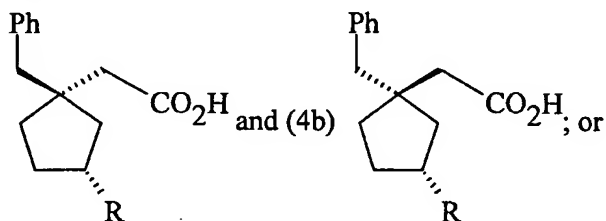


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce

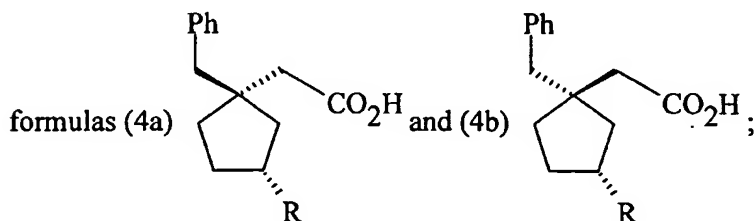
-41-



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic acids of formulas (4a)



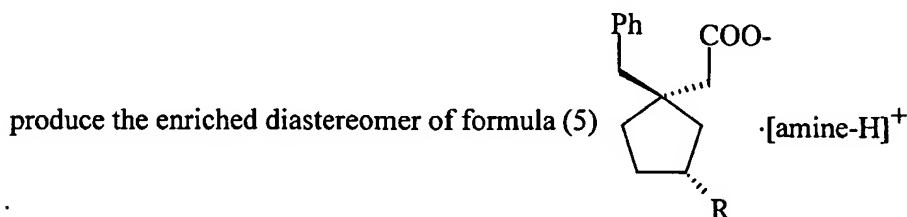
adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of



- d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and

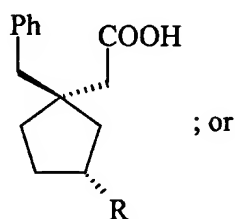
-42-

pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to

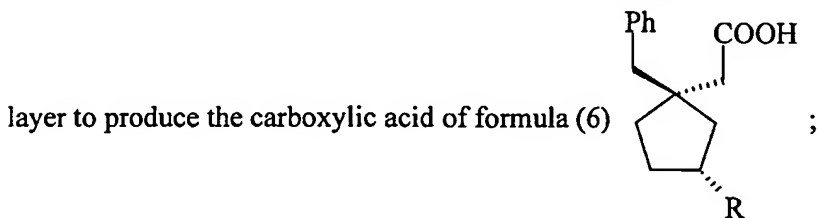


as the amine salt;

- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)



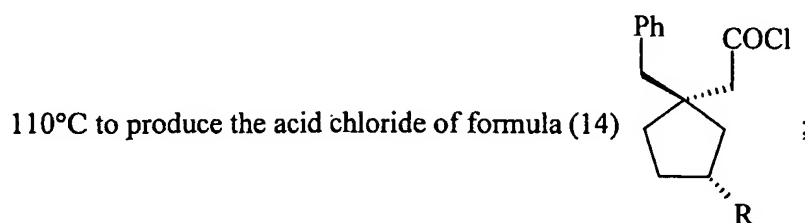
partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic



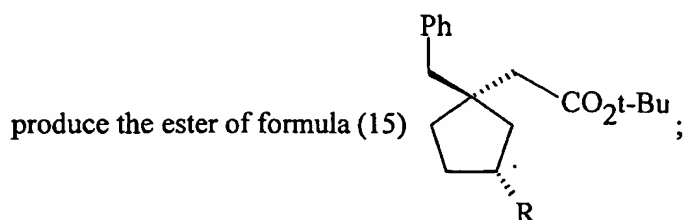
- f) adding oxalyl chloride to a mixture of the product of Step e), a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and 0.01 to 10 mole percent of N,N-

-43-

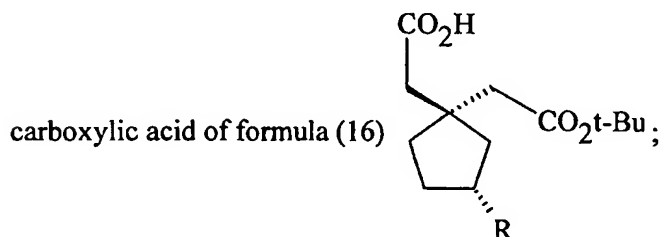
dimethylformamide (DMF), and stirring at a temperature from -40°C to



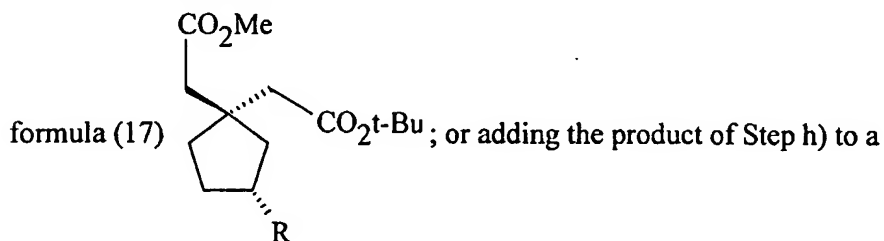
- g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and *N,N*-diisopropylethylamine (DIPEA) or triethylamine, and stirring at a temperature from -40°C to 110°C to



- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the



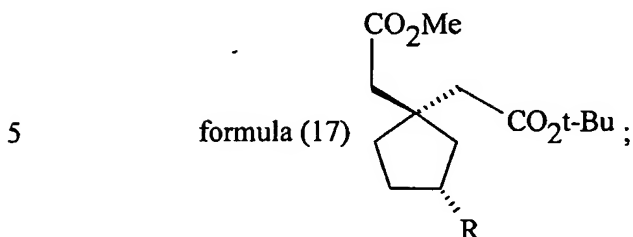
- i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, methanol, and (trimethylsilyl)diazomethane, and stirring at a temperature from 0°C to 150°C to produce the bis ester of



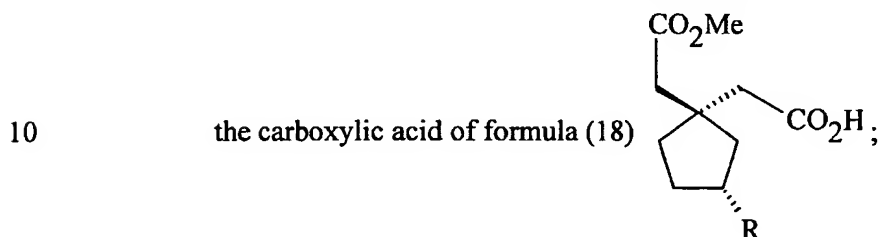
mixture of iodomethane, a solvent selected from dichloromethane,

-44-

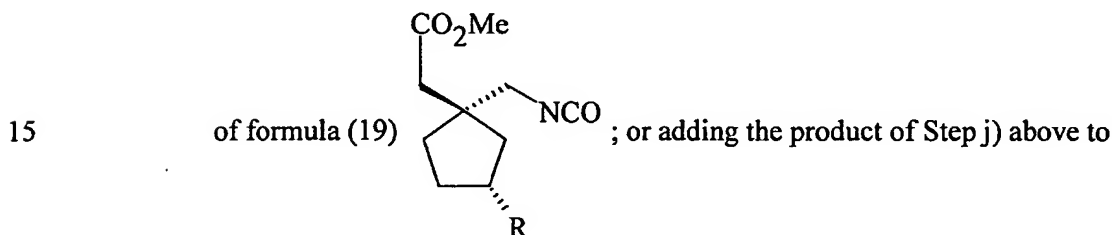
chloroform, tetrahydrofuran, toluene and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and stirring at a temperature of from -40°C to 110°C to produce the bis ester of



- j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and a solvent selected from dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, ethyl ether, and *tert*-butyl methyl ether, and stirring at a temperature from -40°C to 110°C to produce



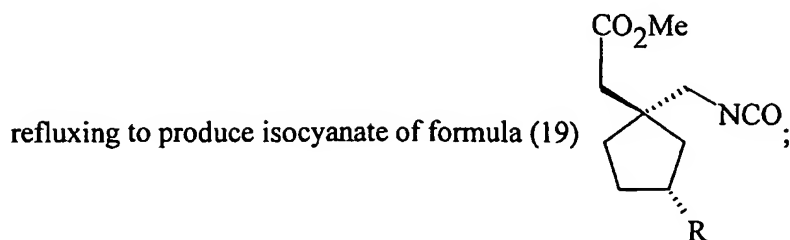
- k) adding the product of Step j) to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature from 0°C to 150°C to produce the isocyanate



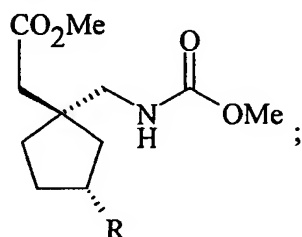
ethyl chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and

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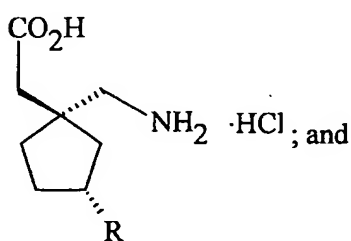
tetrahydrofuran or acetone, followed by adding toluene or benzene, and



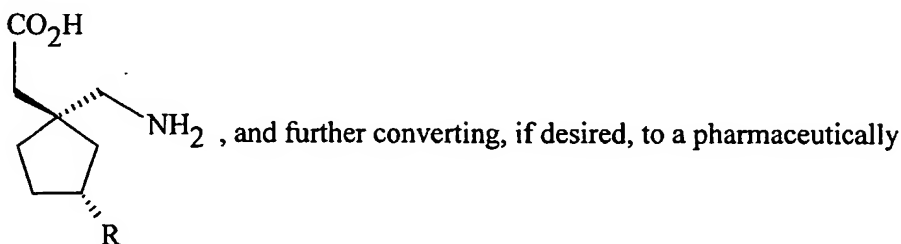
- l) adding the product of Step k) to a mixture of a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (20)



- m) adding the product of Step l) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa



- n) converting the product of Step m) to a compound of Formula II



acceptable salt by known means.

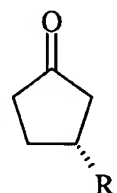
-46-

More preferred is a process for the preparation of a compound of Formula II wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is

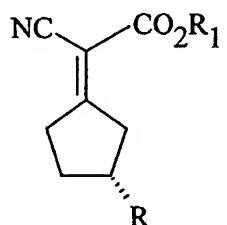
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ethyl, to a mixture of a chiral cyclopentanone of formula (1)



toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark

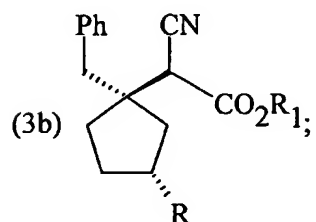
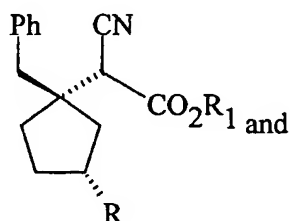
trap to produce the alkene of formula (2)



- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition

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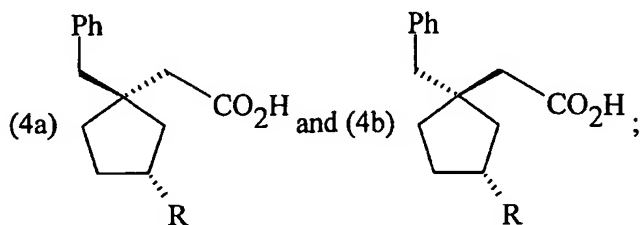
products of formulas (3a)



- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol and heating the mixture at 100°C to 200°C, and then

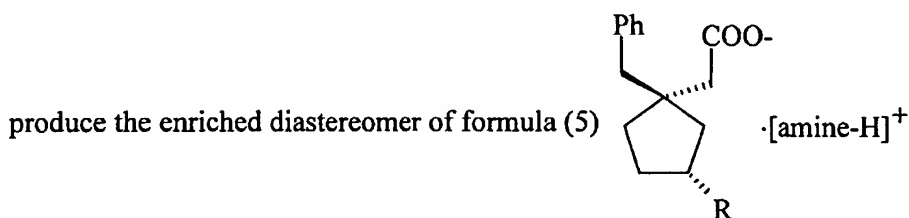
-47-

acidifying to produce the hydrolysis products of formulas



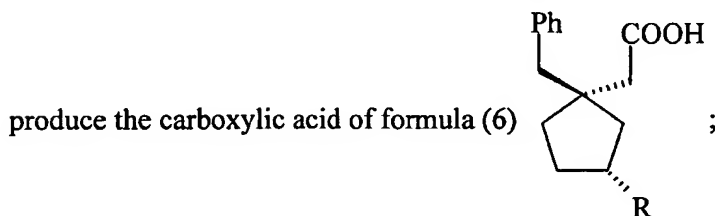
- d) contacting the products of Step c) above with (S)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to

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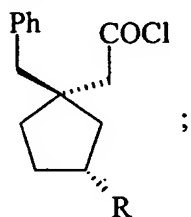
as the (S)- α -methyl-benzylamine salt;

- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to



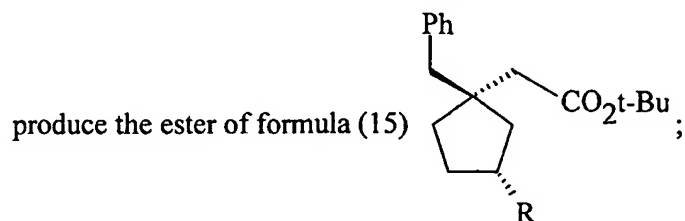
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- f) adding oxalyl chloride to a mixture of the product of Step e), dichloromethane, and a catalytic amount of N,N-dimethylformamide (DMF), and stirring to produce the acid chloride of formula (14)

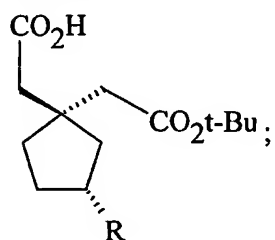


-48-

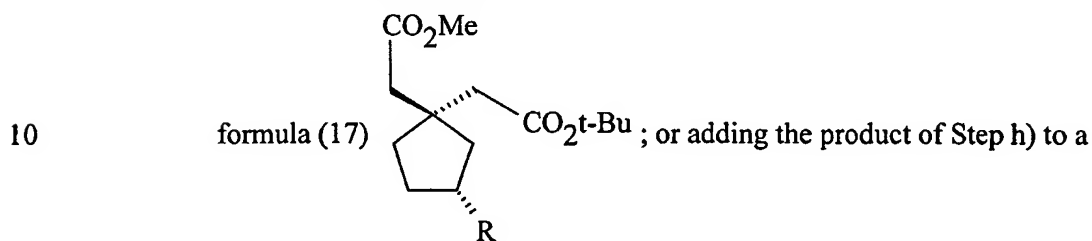
- g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, dichloromethane, and *N,N*-diisopropylethylamine (DIPEA), and stirring to



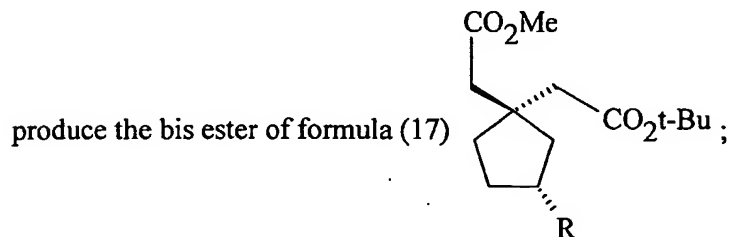
- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (16)



- i) adding the product of Step h) to a mixture of methanol, toluene, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of

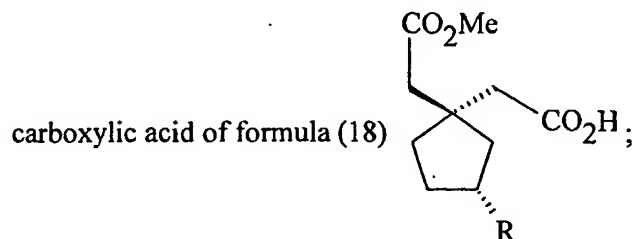


mixture of iodomethane, dichloromethane, triethylamine, and stirring to

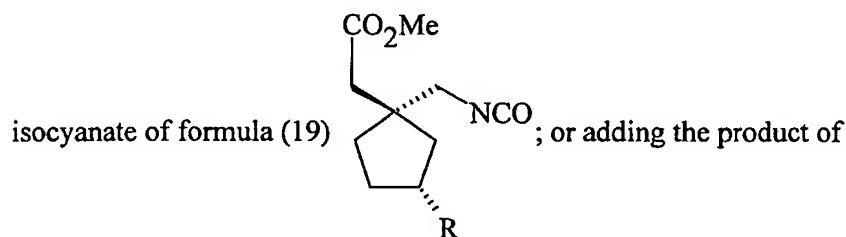


-49-

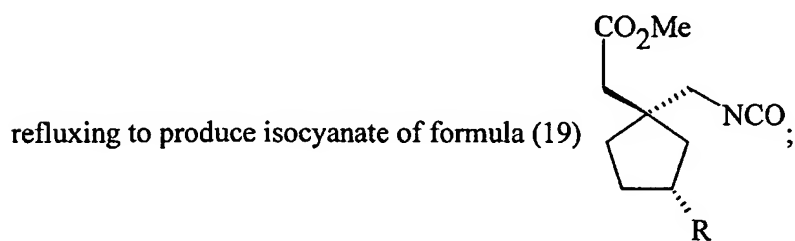
- j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and dichloromethane, and stirring to produce the



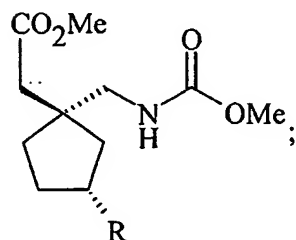
- k) adding the product of Step j) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the



Step j) above to ethyl chloroformate or isobutyl chloroformate, triethylamine, and tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and

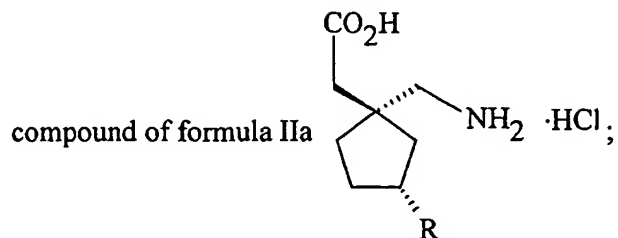


- l) adding the product of Step k) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (20)

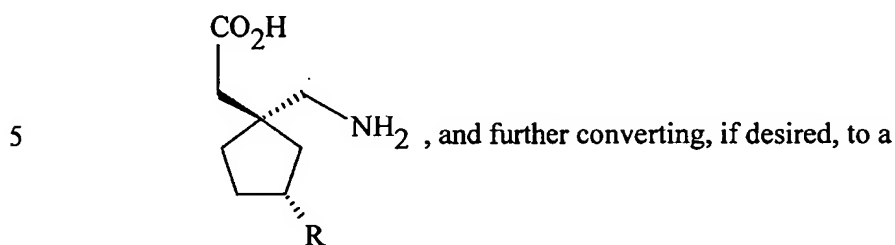


-50-

- m) adding the product of Step l) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a

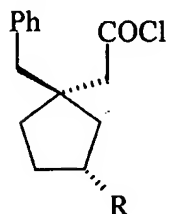


- n) converting the product of Step m) to a compound of Formula II

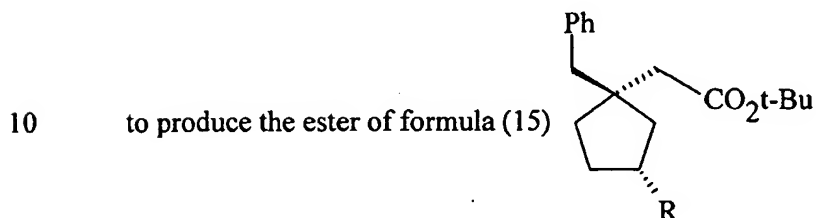


pharmaceutically acceptable salt by known means.

Also preferred is a process for the preparation of a compound of Formula II, further characterized in that the intermediate product (14)

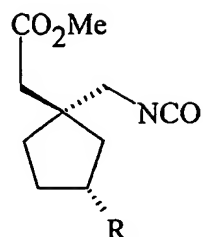


formed is further reacted, without isolation, with *tert*-butyl alcohol



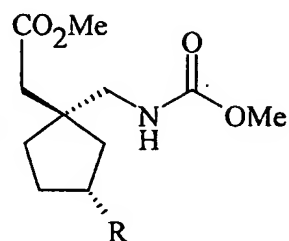
Also preferred is a process for the preparation of a compound of Formula II, further characterized in that the intermediate product (19)

-51-

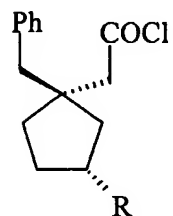


formed is further reacted, without isolation, with methanol to

produce the carbamate of formula (20)

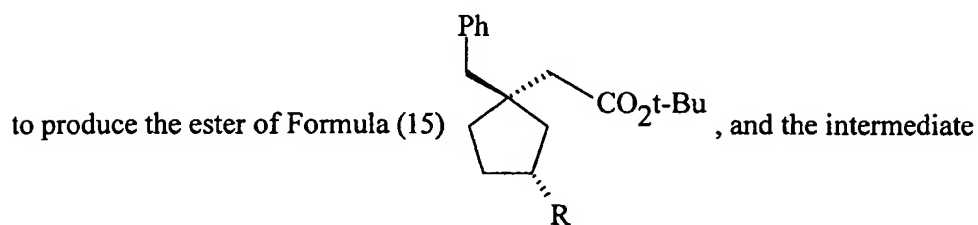


Also preferred is a process for the preparation of a compound of Formula II, further characterized in that the intermediate product (14)

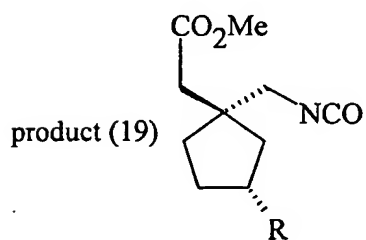


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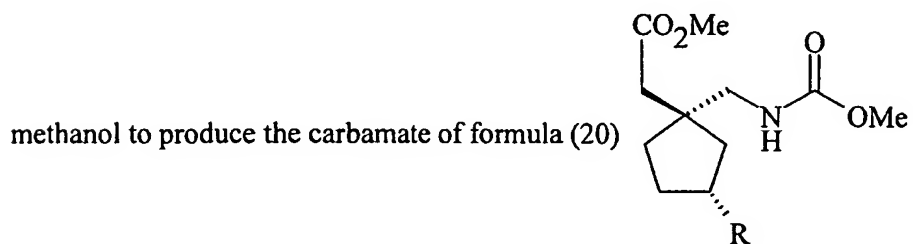
formed is further reacted, without isolation, with *tert*-butyl alcohol



to produce the ester of Formula (15)



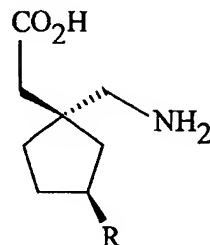
product (19) formed is further reacted, without isolation, with



methanol to produce the carbamate of formula (20)

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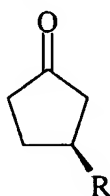
Further, the invention provides a process for the preparation of a compound of Formula III



III

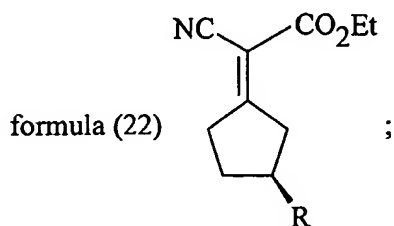
wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)



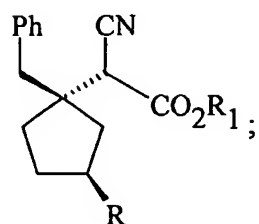
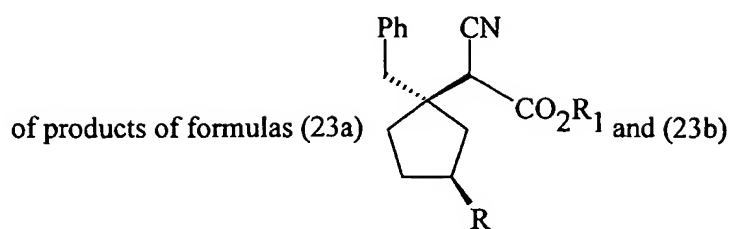
, a solvent, a carboxylic acid, and a Knoevenagel reaction

catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

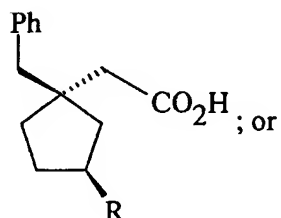
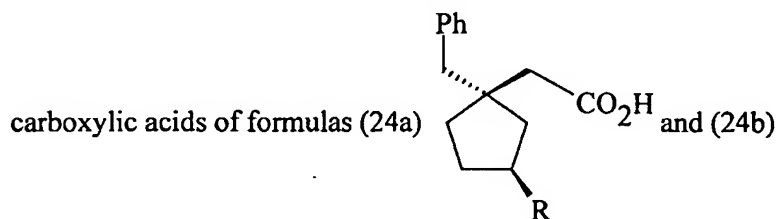


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition

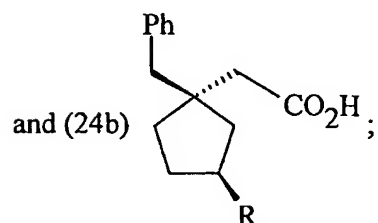
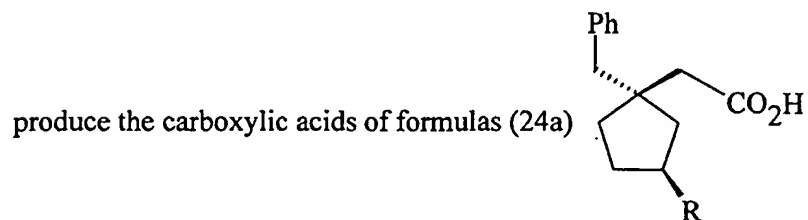
-53-



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

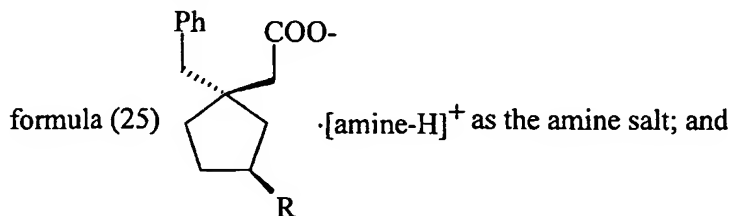


adding the products of Step b) above to an acid mixture, and stirring to

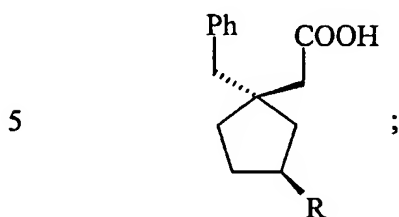


-54-

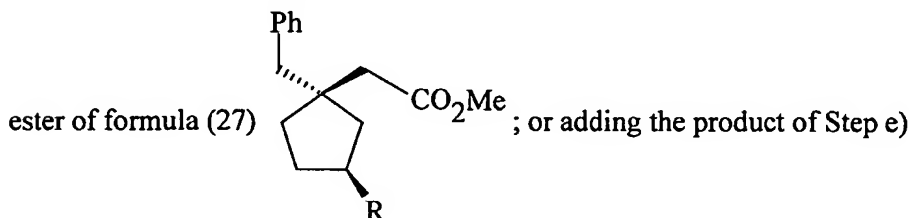
- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



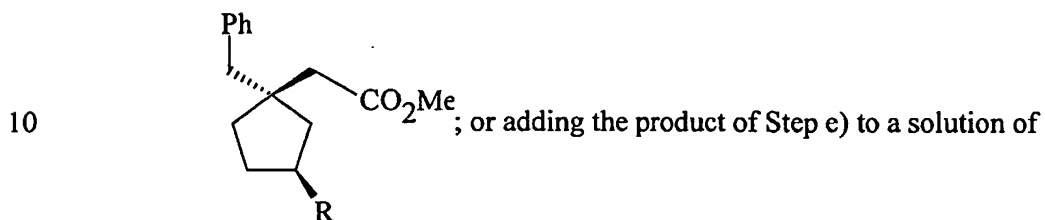
- e) converting the product of Step d) to a carboxylic acid of formula (26)



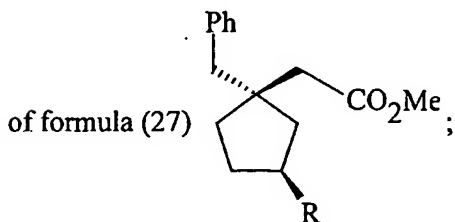
- f) adding the product of Step e) to a mixture of iodomethane, a solvent, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and stirring to produce the



to methanol and an acid to produce the ester of formula (27)



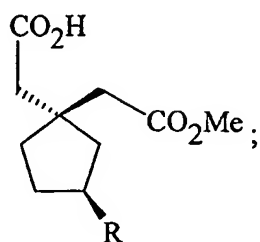
diazomethane or trimethylsilyl-diazomethane in a solvent to produce ester



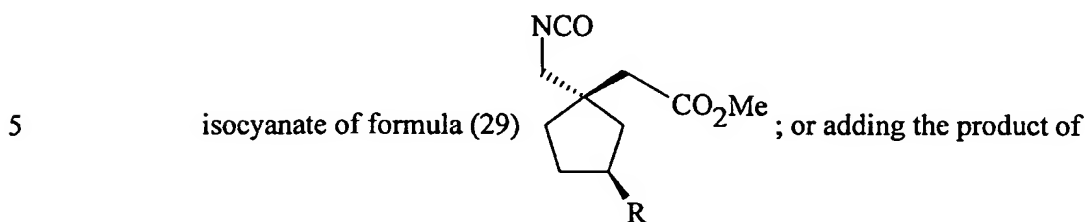
- g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III)

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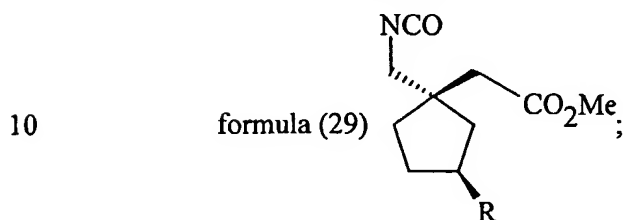
chloride, and stirring to produce the carboxylic acid of formula (28)



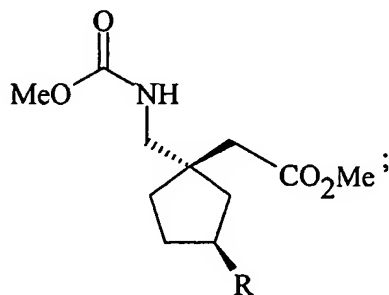
- h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the



Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of

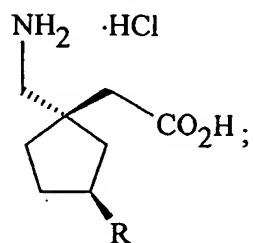


- i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (30)

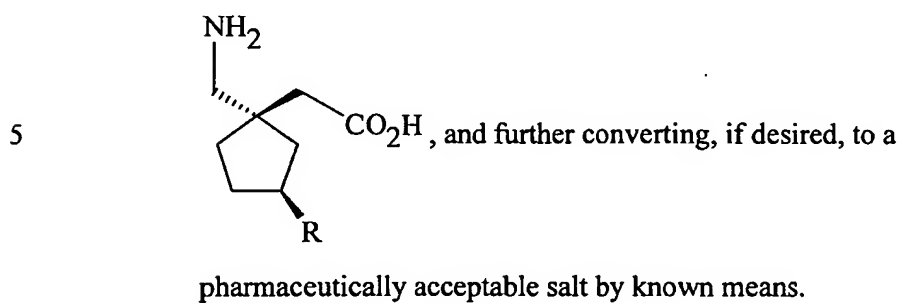


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- j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IIIa)



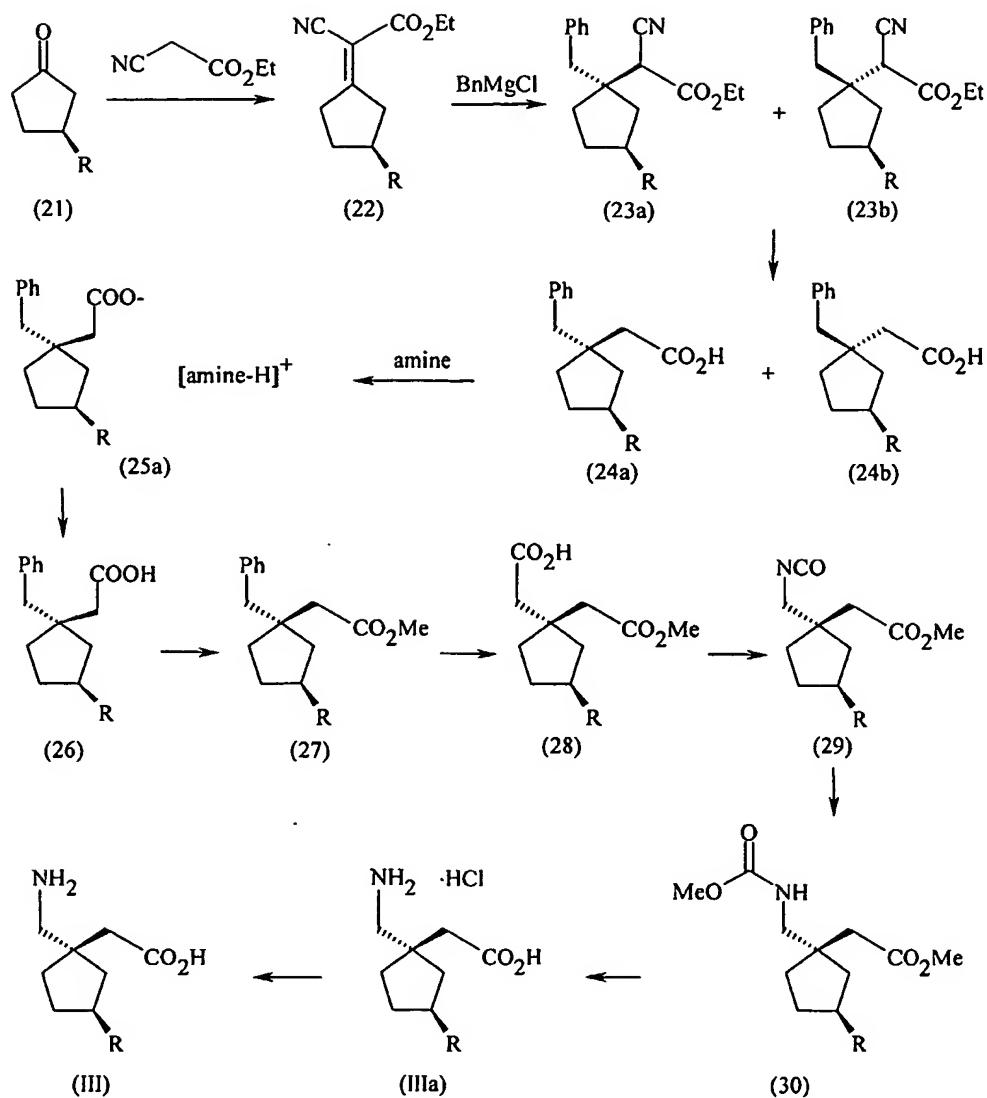
- k) converting the product of Step j) to a compound of formula (III)



This process is outlined in Scheme 4.

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Scheme 4



Preferred is a process for the preparation of a compound of Formula III wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

5

- a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which acetic acid and β-alanine or ammonium acetate were added, and stirring the mixture at a temperature from 0°C to 150°C to produce the alkene of formula (22);

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- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent selected from tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, ethyl ether, or *tert*-butyl methyl ether at a temperature from -100°C to 110°C to produce the addition products of formulas (23a) and (23b);
- 5 c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, or diethylene glycol and stirring the mixture at a temperature from 25°C to 250°C to produce the carboxylic acids of formulas (24a) and (24b);
- 10 d) contacting the products of Step c) above with (R)- α -methyl-benzylamine in a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, or 1,4-dioxane at a temperature from -40°C to 105°C, and recrystallizing the salt so formed from a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, 1,4-dioxane, *tert*-butyl methyl ether, toluene, or *n*-heptane to produce the enriched diastereomer of formula (25a) as the (R)- α -methyl-benzylamine salt;
- 15 e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water was added and stirring at a temperature from -40°C to 115°C to produce the carboxylic acid of formula (26);
- 20 f) adding the product of Step e) to a mixture of iodomethane in a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene, or 1,4-dioxane to which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added, and stirring at a temperature from -40°C to 110°C to produce the ester of formula (27);
- 25 g) adding the product of Step f) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (28);
- 30

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- h) adding the product of Step g) to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which diphenylphosphoryl azide (DPPA) was added, and stirring at a temperature from 0°C to 150°C to produce the isocyanate of formula (29);
- 5 i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol was added and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (30);
- j) adding the product of Step i) to a solvent selected from water, acetic acid, or 1,4-dioxane to which aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M was added, and stirring at a temperature from 0°C to 115°C to produce a compound of Formula IIIa;
- 10 k) converting the product of Step j) to a compound of Formula III, and further converting, if desired, to a pharmaceutically acceptable salt by known means.
- 15

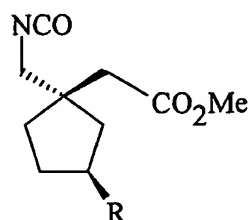
More preferred is a process for the preparation of a compound of Formula III wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in toluene to which acetic acid and ammonium acetate were added, and heating the mixture at reflux to produce the alkene of formula (22);
- 20 b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a) and (23b);
- 25 c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C to produce the hydrolysis products of formulas (24a) and (24b);
- d) contacting the products of Step c) above with (R)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25a) as the (R)- α -methyl-benzylamine salt;
- 30

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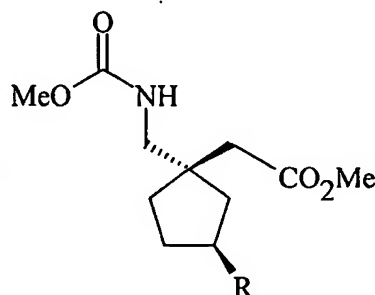
- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26);
- f) adding the product of Step e) to a mixture of iodomethane in dichloromethane to which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added, and stirring to produce the ester of formula (27);
- 5 g) adding the product of Step f) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (28);
- h) adding the product of Step g) to a mixture of triethylamine and toluene to which diphenylphosphoryl azide (DPPA) was added, and refluxing to produce the isocyanate of formula (29);
- 10 i) adding the product of Step h) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (30);
- j) adding the product of Step i) to 1,4-dioxane to which aqueous hydrochloric acid at a concentration of 6 M was added, and stirring to produce a compound of Formula IIIa;
- 15 k) converting the product of Step j) to a compound of Formula III, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

20 Also preferred is a process for the preparation of a compound of Formula III, further characterized in that the intermediate product (29)



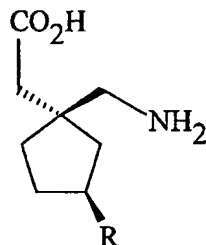
formed is further reacted, without isolation, with methanol to

produce the carbamate of formula (30)



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Further, the invention provides a process for the preparation of a compound of Formula IV

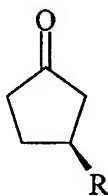


IV

wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

5

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)

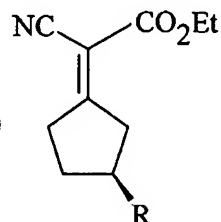


, a solvent, a carboxylic acid, and a Knoevenagel reaction

catalyst, and stirring the mixture in the presence of a means of removing

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water to produce the alkene of formula (22)

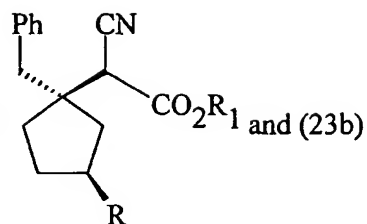


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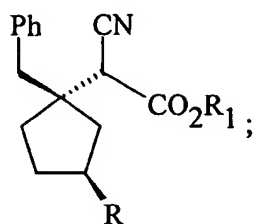
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition

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of products of formulas (23a)

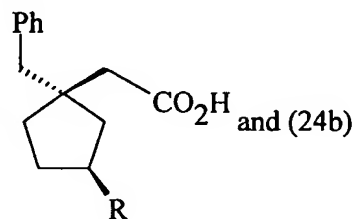


and (23b)

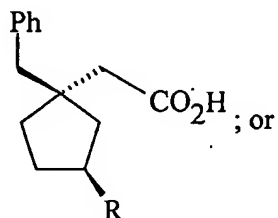


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

carboxylic acids of formulas (24a)

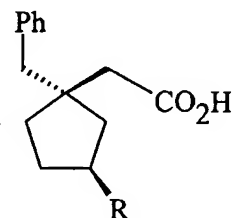


and (24b)

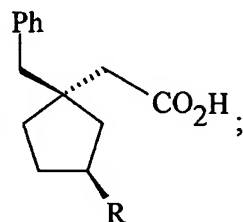


adding the products of Step b) above to an acid mixture, and stirring to

produce the carboxylic acids of formulas (24a)

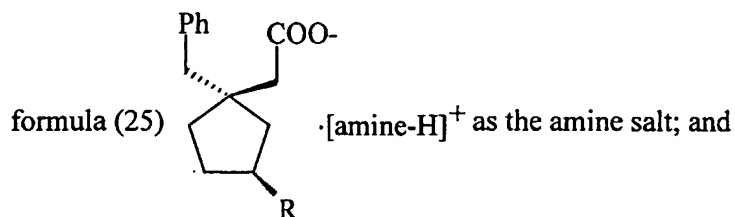


and (24b)

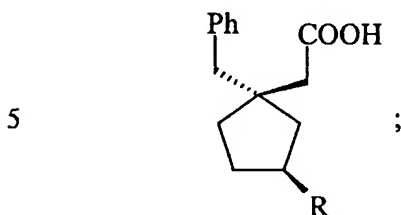


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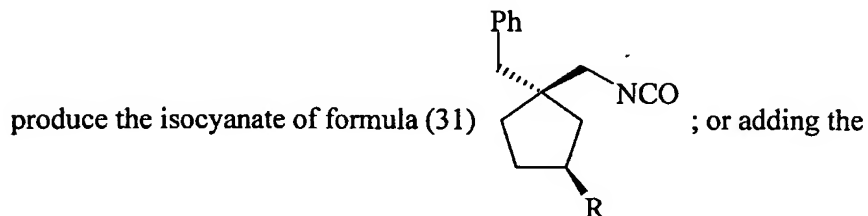
- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



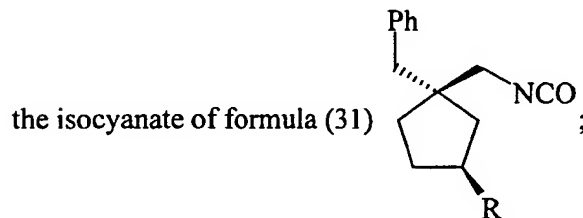
- e) converting the product of Step d) to a carboxylic acid of formula (26)



- f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring to

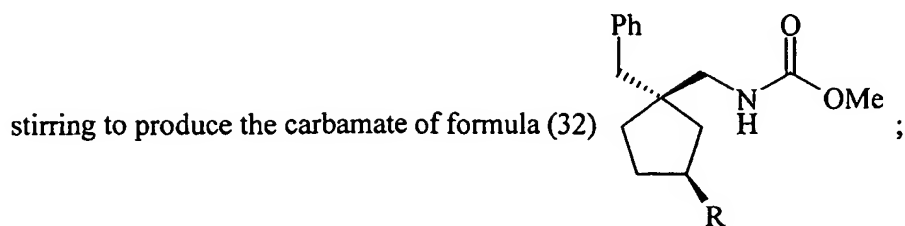


10 product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce

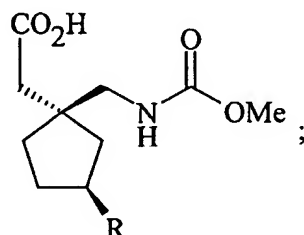


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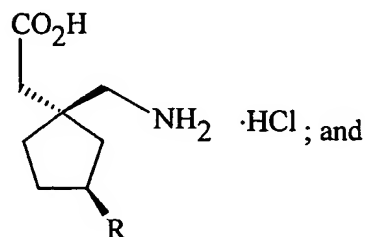
- g) adding the product of Step f) to a mixture of a solvent and methanol, and



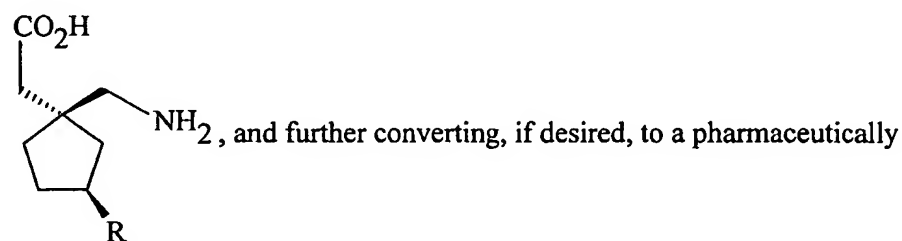
- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (33)



- i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of formula (IVa)



- j) converting the product of Step i) to a compound of formula (IV)

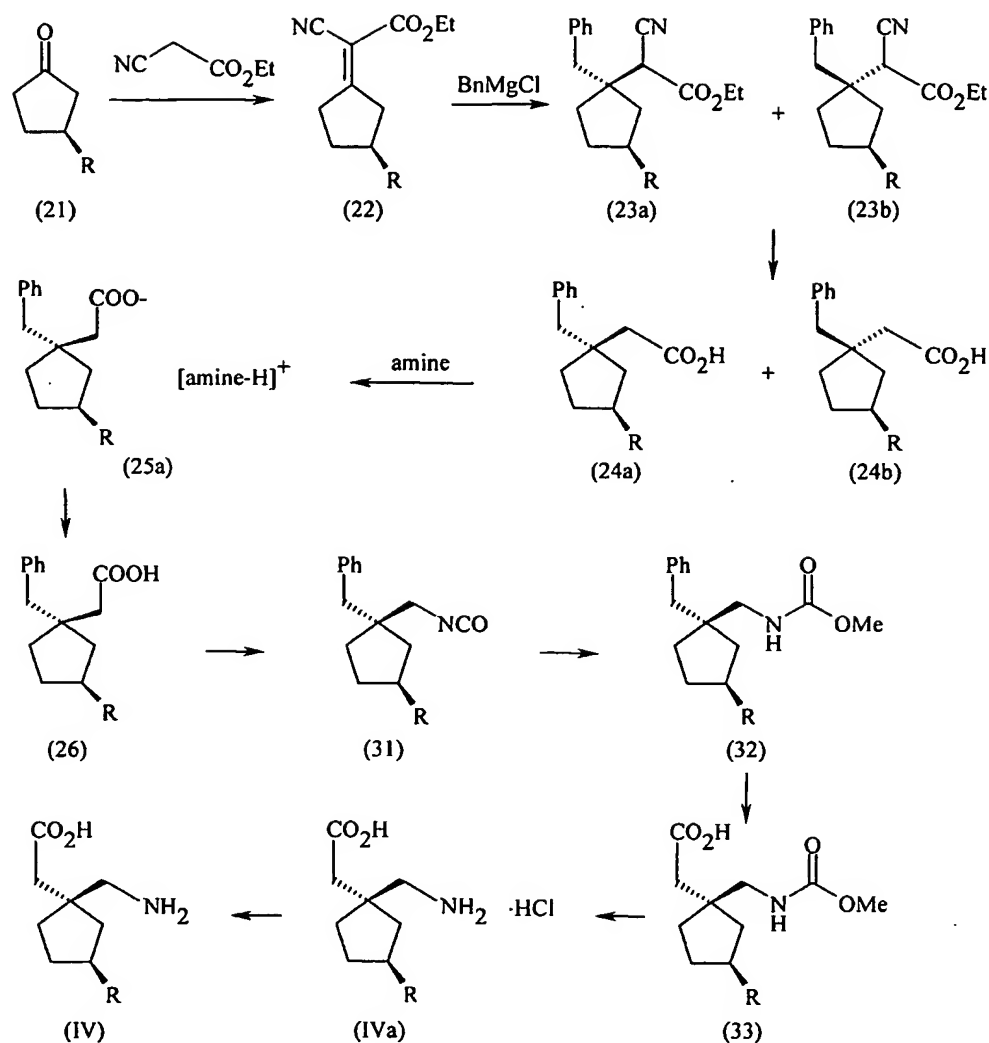


acceptable salt by known means.

This process is outlined in Scheme 5.

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Scheme 5



Preferred is a process for the preparation of a compound of Formula IV wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which acetic acid and β-alanine or ammonium acetate were added, and stirring the mixture at a temperature from 0°C to 150°C to produce the alkene of formula (22);
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent selected from tetrahydrofuran, 1,4-dioxane,

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n-heptane, toluene, ethyl ether, or *tert*-butyl methyl ether at a temperature from -100°C to 110°C to produce the addition products of formulas (23a) and (23b);

- 5 c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, or diethylene glycol and stirring the mixture at a temperature from 25°C to 250°C to produce the carboxylic acids of formulas (24a) and (24b);
- 10 d) contacting the products of Step c) above with (R)- α -methyl-benzylamine in a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, or 1,4-dioxane at a temperature from -40°C to 105°C, and recrystallizing the salt so formed from a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, 1,4-dioxane, *tert*-butyl methyl ether, toluene, or *n*-heptane to produce the enriched diastereomer of formula (25a) as the (R)- α -methyl-benzylamine salt;
- 15 e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water was added and stirring at a temperature from -40°C to 115°C to produce the carboxylic acid of formula (26);
- 20 f) adding the product of Step e) to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which diphenylphosphoryl azide (DPPA) was added, and stirring at a temperature from 0°C to 150°C to produce the isocyanate of formula (31);
- 25 g) adding the product of Step f) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol was added and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (32);
- 30 h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride

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were added, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (33);

- i) adding the product of Step h) to a solvent selected from water, acetic acid, or 1,4-dioxane to which aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M was added, and stirring at a temperature from 0°C to 115°C to produce a compound of Formula IVa;
- j) converting the product of Step i) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

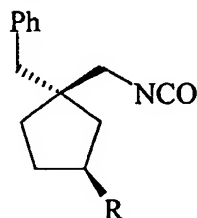
More preferred is a process for the preparation of a compound of Formula IV wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in toluene to which acetic acid and ammonium acetate were added, and heating the mixture at reflux to produce the alkene of formula (22);
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a) and (23b);
- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C to produce the hydrolysis products of formulas (24a) and (24b);
- d) contacting the products of Step c) above with (R)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25a) as the (R)- α -methyl-benzylamine salt;
- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26);
- f) adding the product of Step e) to a mixture of triethylamine and toluene to which diphenylphosphoryl azide (DPPA) was added, and refluxing to produce the isocyanate of formula (31);
- g) adding the product of Step f) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (32);

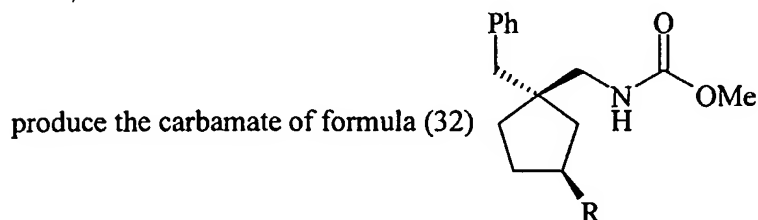
-68-

- h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (33);
- i) adding the product of Step h) to 1,4-dioxane to which aqueous hydrochloric acid at a concentration of 6 M was added, and stirring to produce a compound of Formula IVa;
- j) converting the product of Step i) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (31)

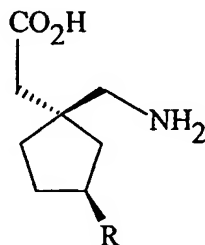


formed is further reacted, without isolation, with methanol to



produce the carbamate of formula (32)

Still further, the invention provides a process for the preparation of a compound of Formula IV

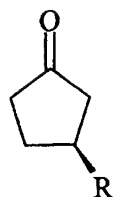


IV

wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

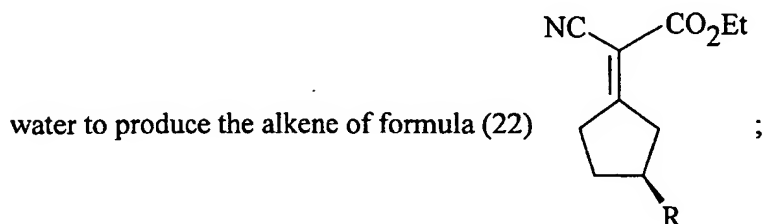
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)

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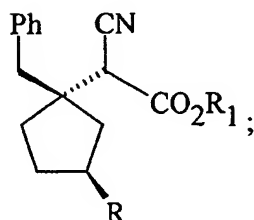
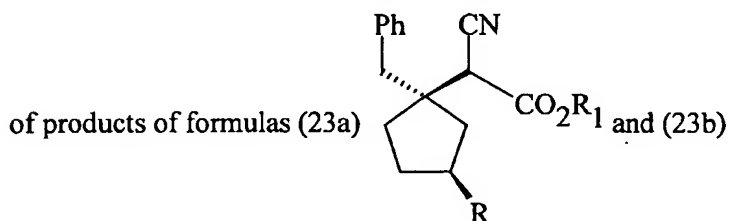


, a solvent, a carboxylic acid, and a Knoevenagel reaction

catalyst, and stirring the mixture in the presence of a means of removing

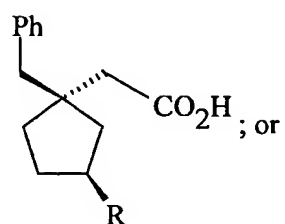
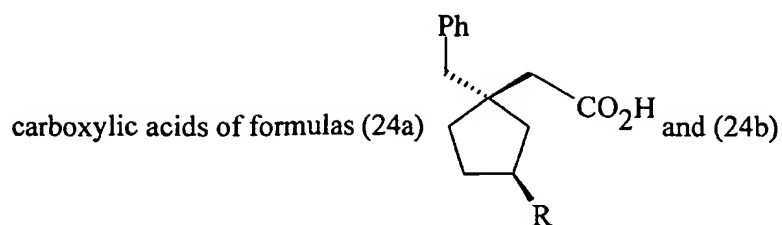


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition

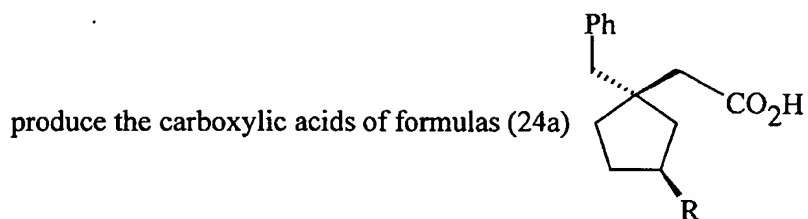


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying to produce the

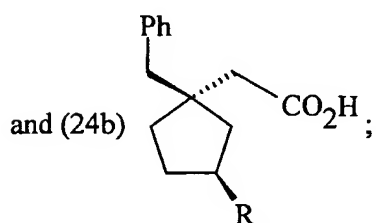
-70-



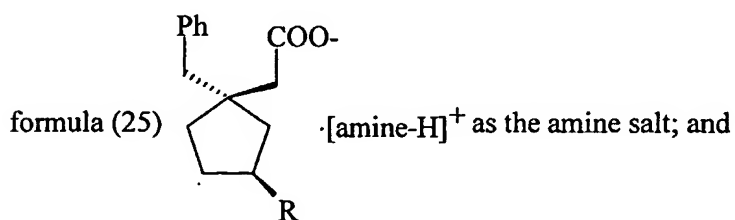
adding the products of Step b) above to an acid mixture, and stirring to



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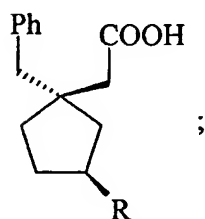


- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



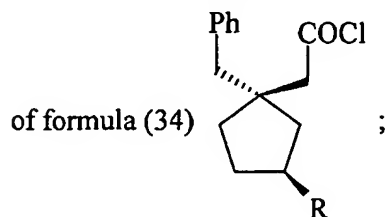
- e) converting the product of Step d) to a carboxylic acid of formula (26)

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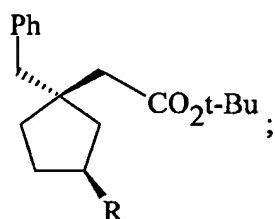


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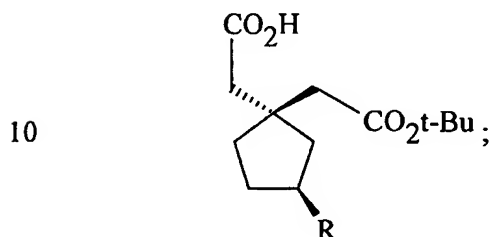
- f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce the acid chloride



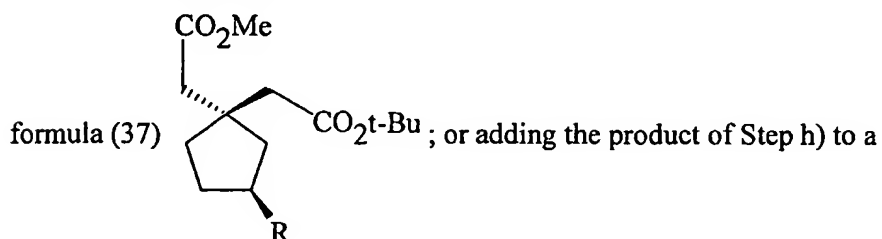
- 5 g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of formula (35)



- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of formula (36)

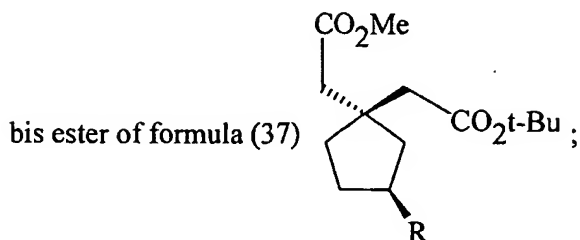


- i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of

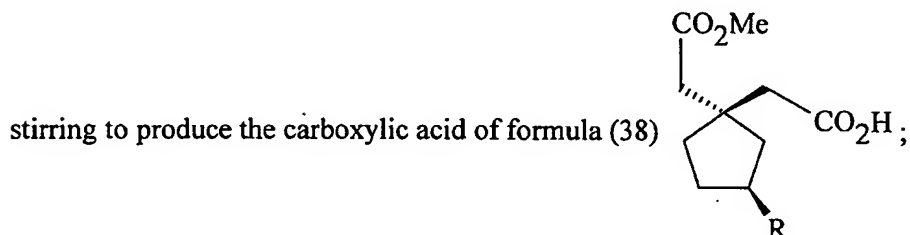


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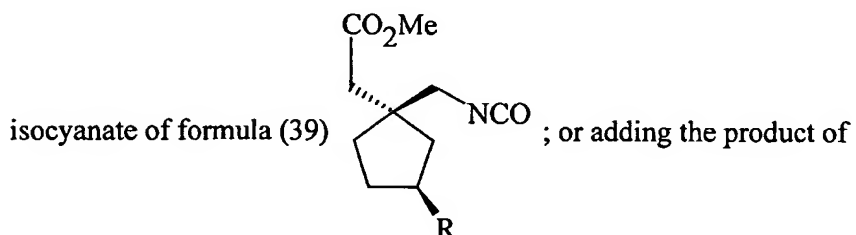
mixture of iodomethane, a solvent, and a base, and stirring to produce the



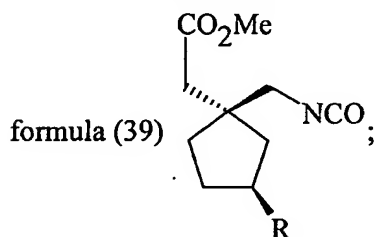
j) adding an acid to a mixture of the product from Step i) and a solvent and



5 k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to produce the

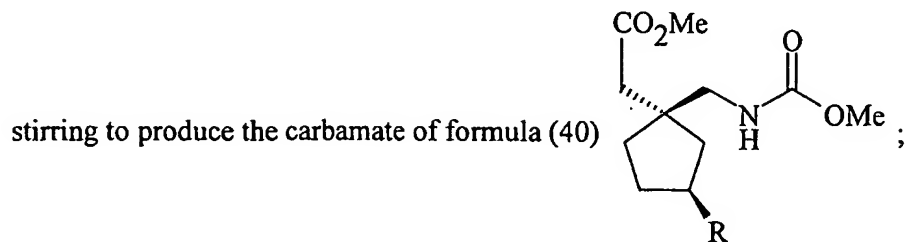


Step j) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of

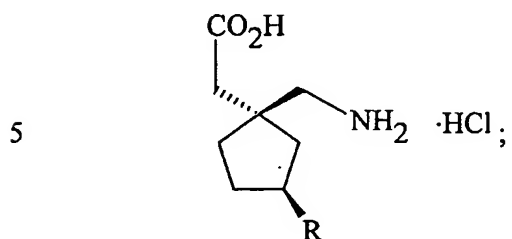


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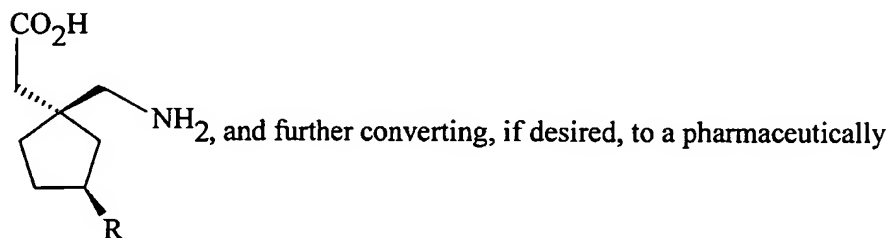
- l) adding the product of Step k) to a mixture of a solvent and methanol, and



- m) adding the product of Step l) to a mixture of a solvent and hydrochloric acid, and stirring to produce a compound of formula (IVa)



- n) converting the product of Step m) to a compound of Formula IV

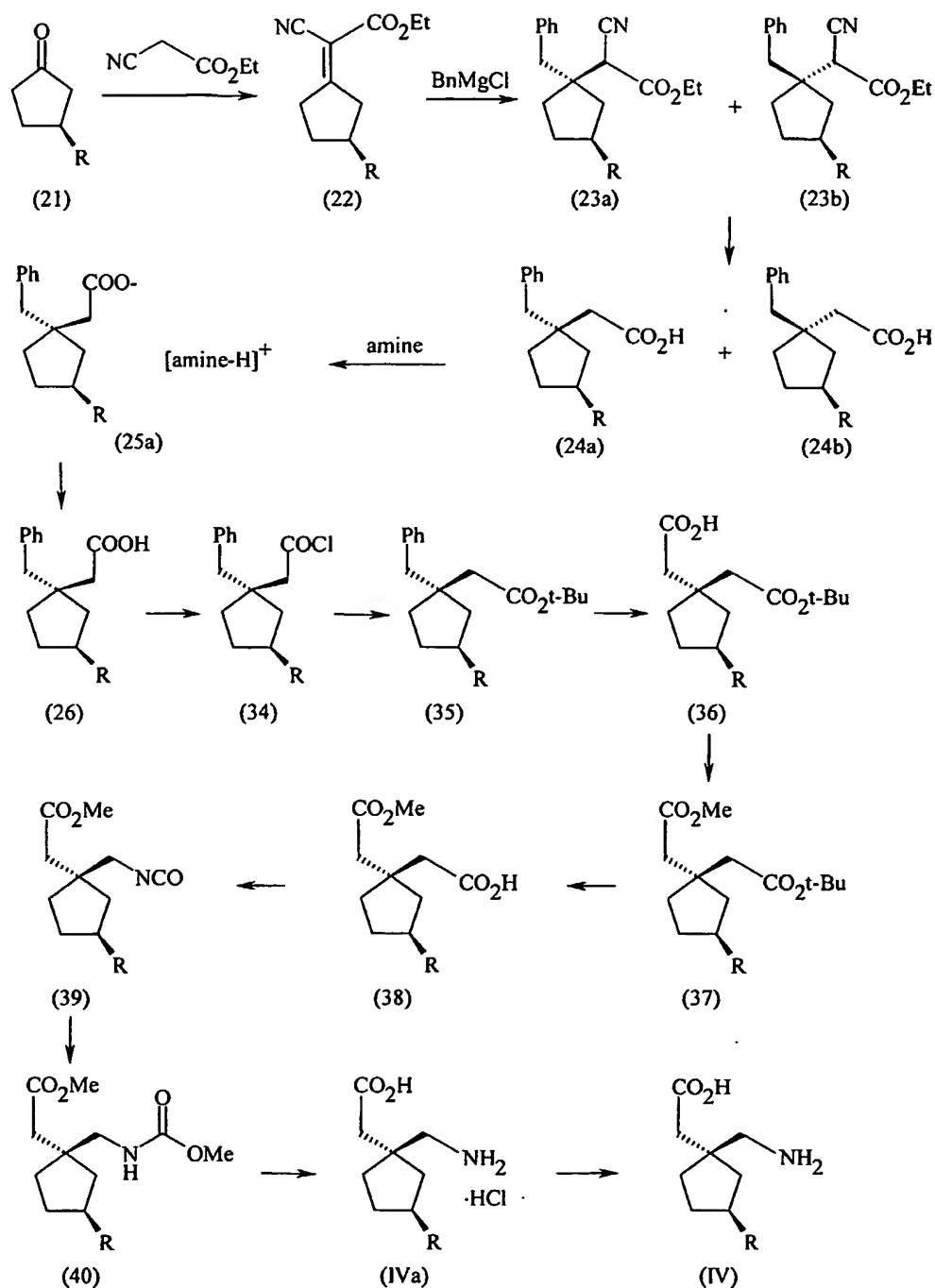


acceptable salt by known means.

This process is outlined in Scheme 6.

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Scheme 6



Preferred is a process for the preparation of a compound of Formula IV wherein R is $\text{C}_1\text{-C}_{10}$ alkyl or $\text{C}_3\text{-C}_{10}$ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

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- a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which acetic acid and β -alanine or ammonium acetate were added, and stirring the mixture at a temperature from 0°C to 150°C to produce the alkene of formula (22);
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent selected from tetrahydrofuran, 1,4-dioxane, *n*-heptane, toluene, ethyl ether, or *tert*-butyl methyl ether at a temperature from -100°C to 110°C to produce the addition products of formulas (23a) and (23b);
- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, or diethylene glycol and stirring the mixture at a temperature from 25°C to 250°C to produce the carboxylic acids of formulas (24a) and (24b);
- d) contacting the products of Step c) above with (R)- α -methyl-benzylamine in a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, or 1,4-dioxane at a temperature from -40°C to 105°C, and recrystallizing the salt so formed from a solvent selected from ethyl acetate, acetonitrile, tetrahydrofuran, 1,4-dioxane, *tert*-butyl methyl ether, toluene, or *n*-heptane to produce the enriched diastereomer of formula (25a) as the (R)- α -methyl-benzylamine salt;
- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water was added and stirring at a temperature from -40°C to 115°C to produce the carboxylic acid of formula (26);
- f) adding oxalyl chloride to a mixture of the product of Step e) and a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, or *tert*-butyl methyl ether to which 0.01 mol percent to 10 mol percent of N,N-

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dimethylformamide (DMF) was added, and stirring at a temperature from -40°C to 110°C to produce the acid chloride of formula (34);

g) adding the product of Step f) to a mixture of *tert*-butyl alcohol in a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, or *tert*-butyl methyl ether to which *N,N*-diisopropylethylamine (DIPEA) or triethylamine was added, and stirring at a temperature from -40°C to 110°C to produce the ester of formula (35);

h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (36);

i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol and (trimethylsilyl)diazomethane were added, and stirring at a temperature from 0°C to 150°C to produce the bis ester of formula (37);

j) adding trifluoroacetic acid (TFA) to a mixture of the product from Step i) and a solvent selected from dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, ethyl ether, or *tert*-butyl methyl ether and stirring at a temperature from -40°C to 110°C to produce the carboxylic acid of formula (38);

k) adding the product of Step j) to a mixture of a base selected from triethylamine or diisopropylethylamine and a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which diphenylphosphoryl azide (DPPA) was added, and stirring at a temperature from 0°C to 150°C to produce the isocyanate of formula (39);

l) adding the product of Step k) to a solvent selected from toluene, benzene, xylenes, or *n*-heptane to which methanol was added and stirring at a temperature from 0°C to 150°C to produce the carbamate of formula (40);

m) adding the product of Step l) to a solvent selected from water, acetic acid, or 1,4-dioxane to which aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M was added, and stirring at a temperature from 0°C to 115°C to produce a compound of Formula IVa;

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- n) converting the product of Step m) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

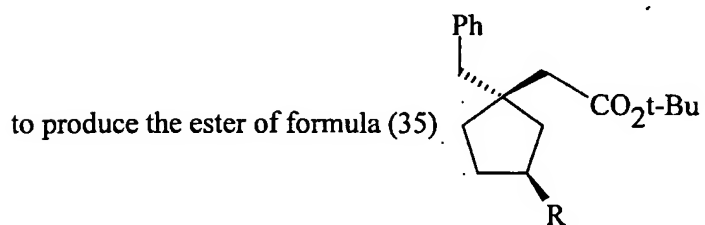
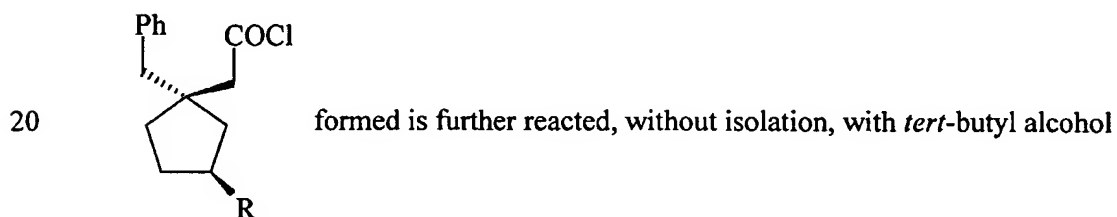
5 More preferred is a process for the preparation of a compound of Formula IV wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (21) in toluene to which acetic acid and ammonium acetate were added, and heating the mixture at reflux to produce the alkene of formula (22);
- 10 b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a) and (23b);
- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C to produce the
- 15 hydrolysis products of formulas (24a) and (24b);
- d) contacting the products of Step c) above with (R)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25a) as the (R)- α -methyl-benzylamine salt;
- 20 e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26);
- f) adding oxalyl chloride to a mixture of the product of Step e) and dichloromethane to which a catalytic amount of N,N-dimethylformamide (DMF) was added, and stirring to produce the acid chloride of formula (34);
- 25 g) adding the product of Step f) to a mixture of *tert*-butyl alcohol in dichloromethane to which *N,N*-diisopropylethylamine (DIPEA) was added, and stirring to produce the ester of formula (35);
- h) adding the product of Step g) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride
- 30 were added, and stirring to produce the carboxylic acid of formula (36);

-78-

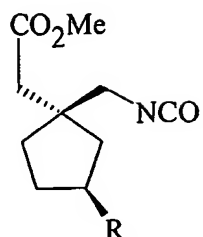
- i) adding the product of Step h) to a mixture of methanol and toluene to which (trimethylsilyl)diazomethane was added, and stirring to produce the bis ester of formula (37);
- 5 j) adding trifluoroacetic acid (TFA) to a mixture of the product from Step i) and dichloromethane, and stirring to produce the carboxylic acid of formula (38);
- k) adding the product of Step j) to a mixture of triethylamine and toluene to which diphenylphosphoryl azide (DPPA) was added, and refluxing to produce the isocyanate of formula (39);
- 10 l) adding the product of Step k) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (40);
- m) adding the product of Step l) to 1,4-dioxane to which aqueous hydrochloric acid at a concentration of 6 M was added, and stirring to produce a compound of Formula IVa;
- 15 n) converting the product of Step m) to a compound of Formula IV, and further converting, if desired, to a pharmaceutically acceptable salt by known means.

Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (34)



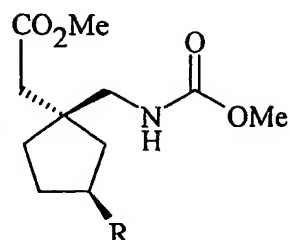
Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (39)

-79-

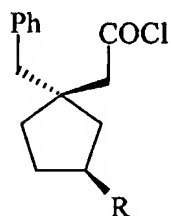


formed is further reacted, without isolation, with methanol to

produce the carbamate of formula (40)

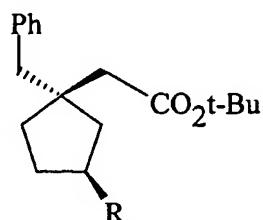


Also preferred is a process for the preparation of a compound of Formula IV, further characterized in that the intermediate product (34)

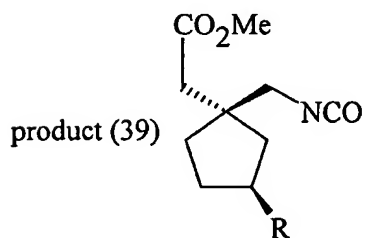


formed is further reacted, without isolation, with *tert*-butyl alcohol

to produce the ester of formula (35)

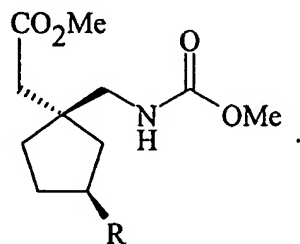


and the intermediate



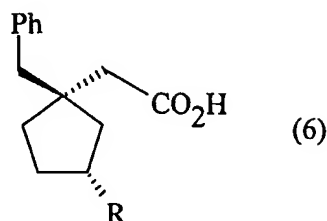
product (39) formed is further reacted, without isolation, with

methanol to produce the carbamate of formula (40)



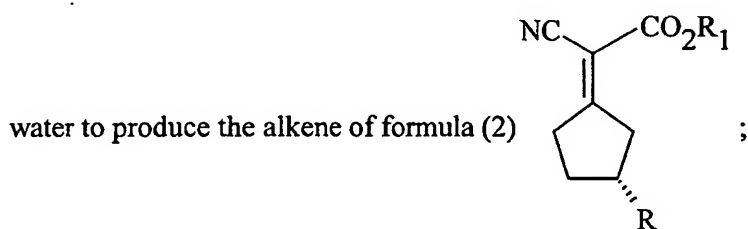
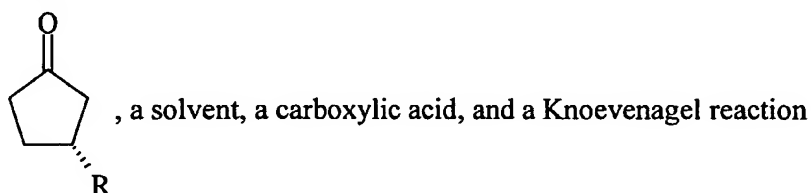
-80-

Further, the invention provides a process for the preparation of a compound of formula (6)

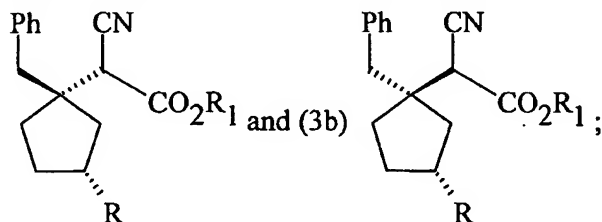


wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (1)

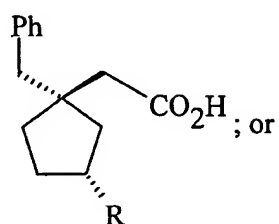
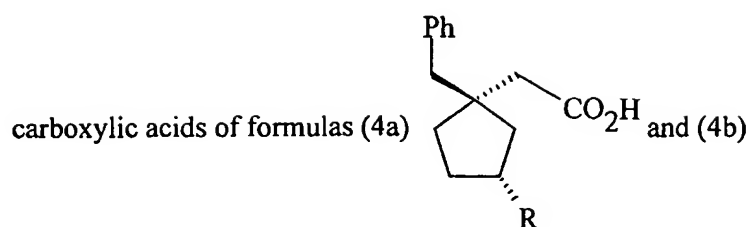


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition products of formulas (3a)

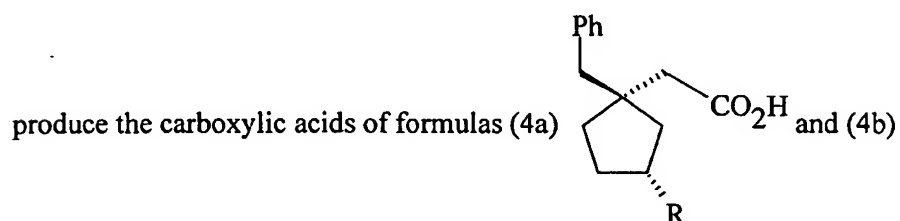


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the

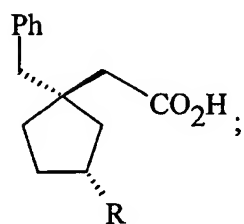
-81-



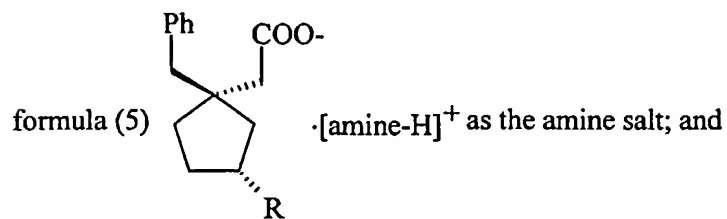
adding the products of Step b) above to an acid mixture and stirring to



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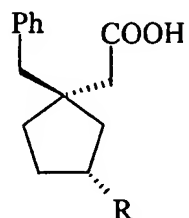


- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



- e) converting the product of Step d) to a carboxylic acid of formula (6)

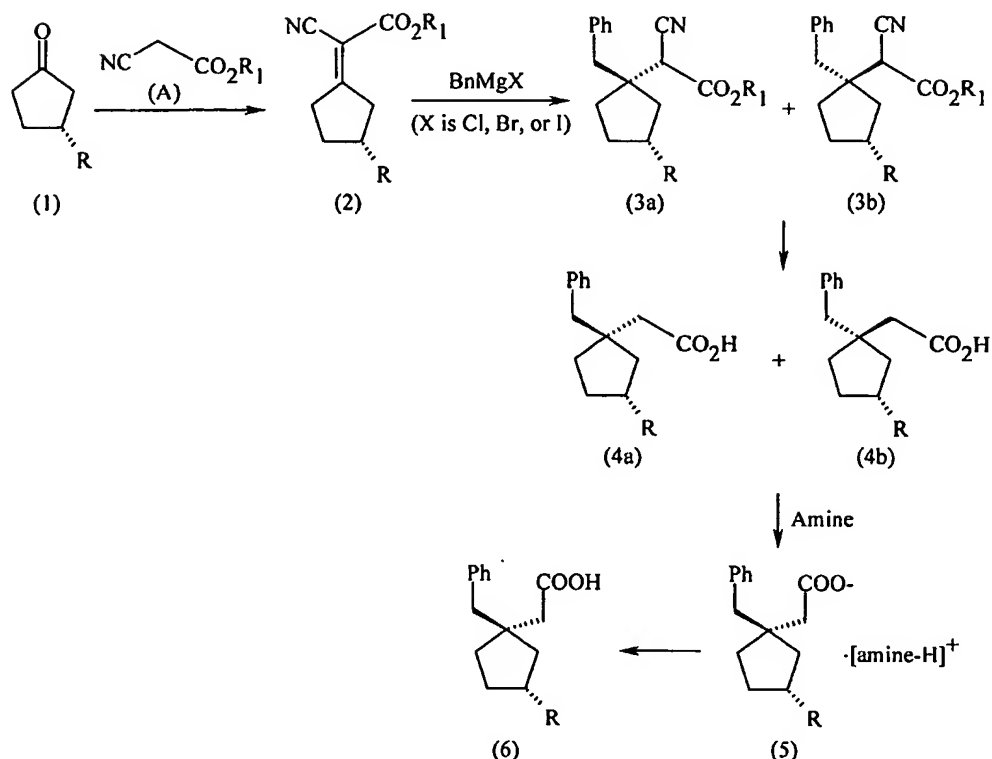
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-82-

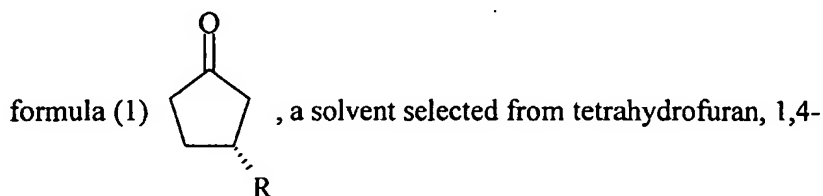
This process is outlined in Scheme 7.

Scheme 7



Preferred is a process for the preparation of a compound of formula (6) wherein R is $\text{C}_1\text{-C}_{10}$ alkyl or $\text{C}_3\text{-C}_{10}$ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

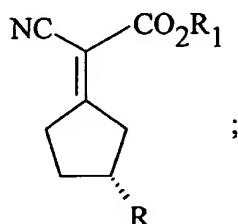
- adding a cyanoacetate of formula (A) $\text{NC-CH}_2\text{-CO}_2\text{R}_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral cyclopentanone of



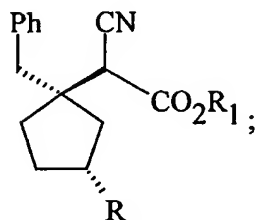
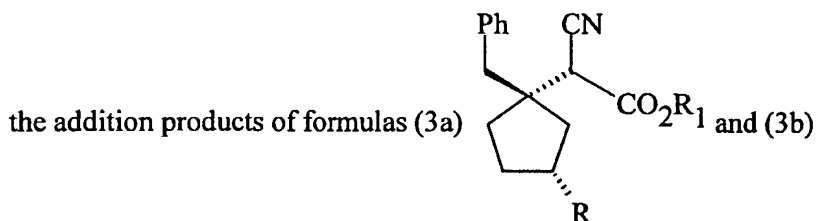
dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and

-83-

n-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)



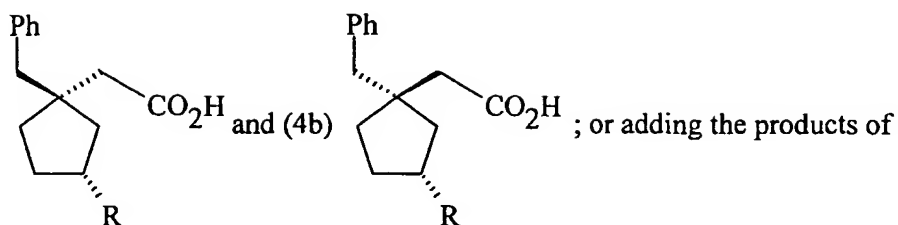
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce



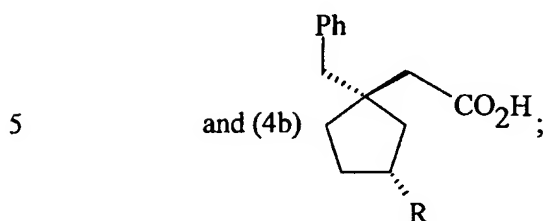
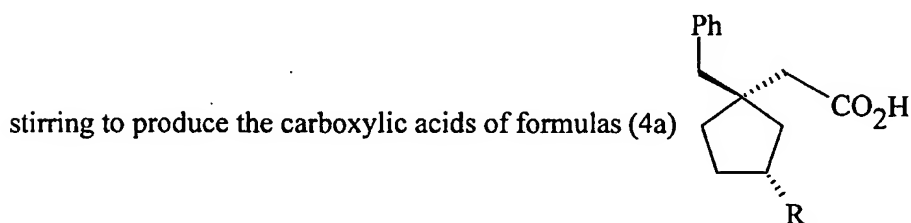
- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (4a)

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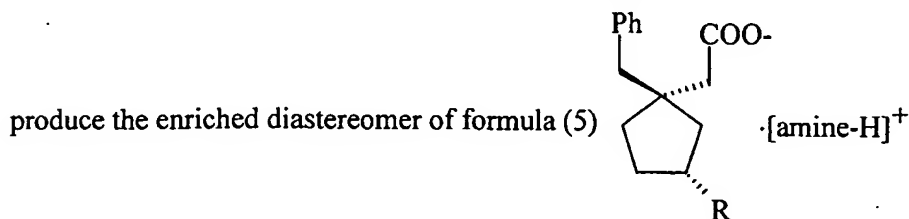
-84-



Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and



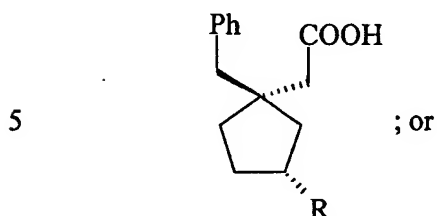
- d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to
- 10
- 15



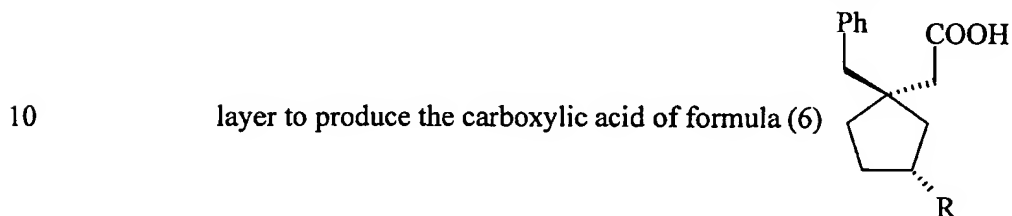
as the amine salt; and

-85-

- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the carboxylic acid of formula (6)

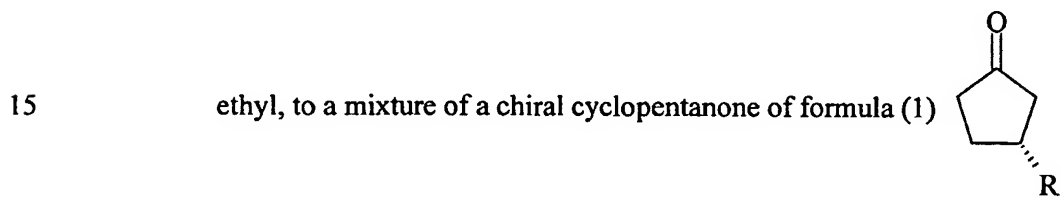


partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic



More preferred is a process for the preparation of a compound of formula (6) wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

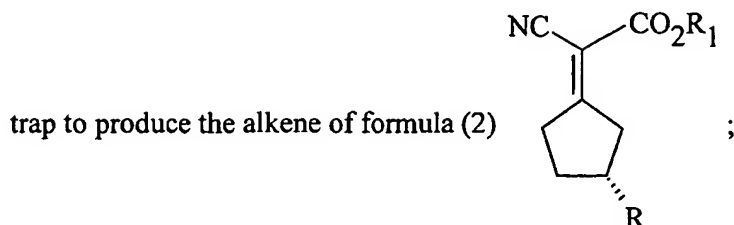
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is



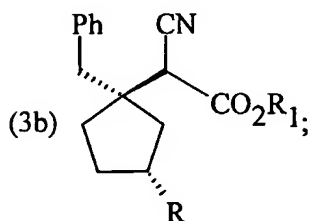
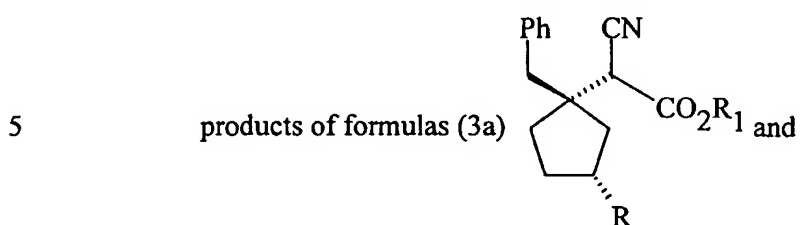
toluene, acetic acid, and a Knoevenagel reaction catalyst which is

-86-

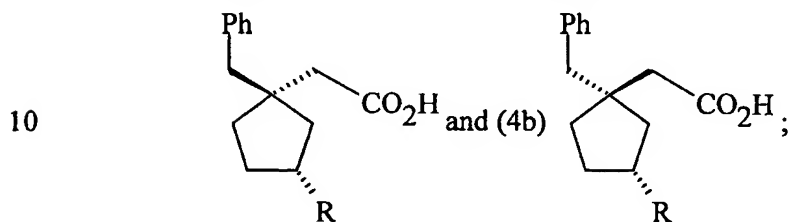
ammonium acetate, and heating the mixture at reflux over a Dean-Stark



- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C to produce the addition

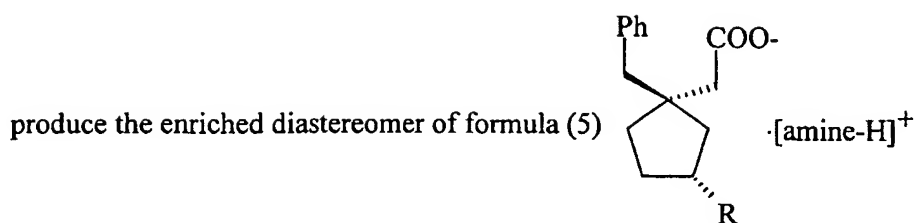


- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (4a)



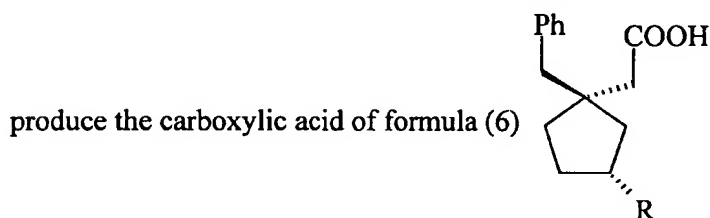
- d) contacting the products of Step c) above with (S)-α-methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to

-87-

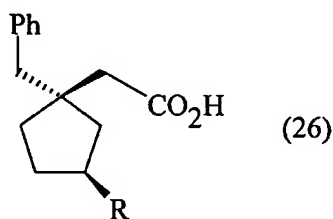


as the (S)- α -methyl-benzylamine salt;

- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to

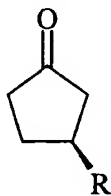


- 5 Further, the invention provides a process for the preparation of a compound of formula (26)



wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

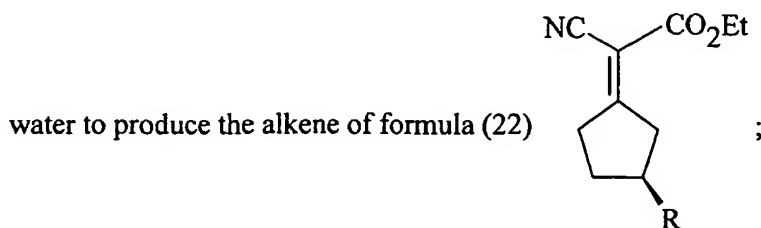
- 10 a) adding a cyanoacetate of formula (A) NC-CH₂-CO₂R₁, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of formula (21)



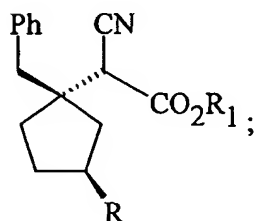
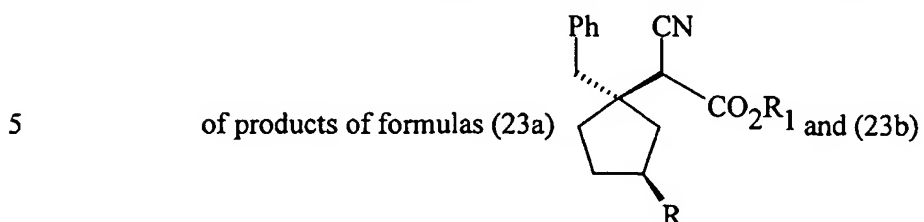
, a solvent, a carboxylic acid, and a Knoevenagel reaction

-88-

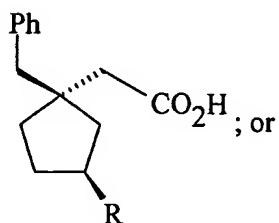
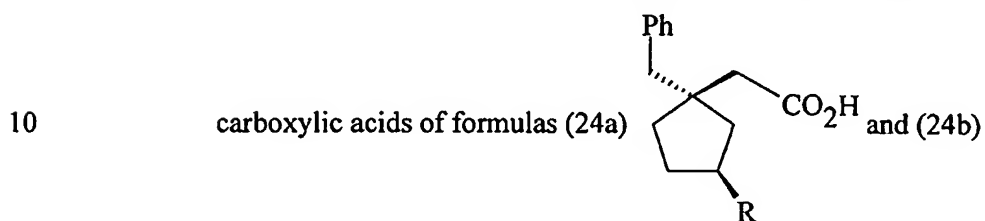
catalyst, and stirring the mixture in the presence of a means of removing



- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition

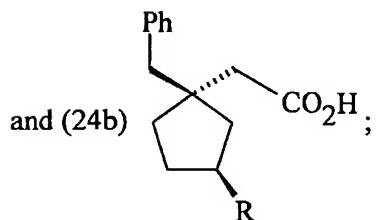
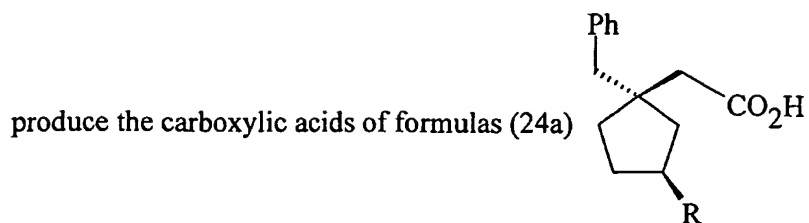


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the

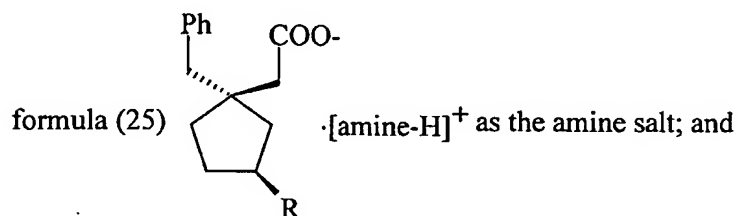


-89-

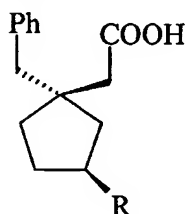
adding the products of Step b) above to an acid mixture, and stirring to



- 5 d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of



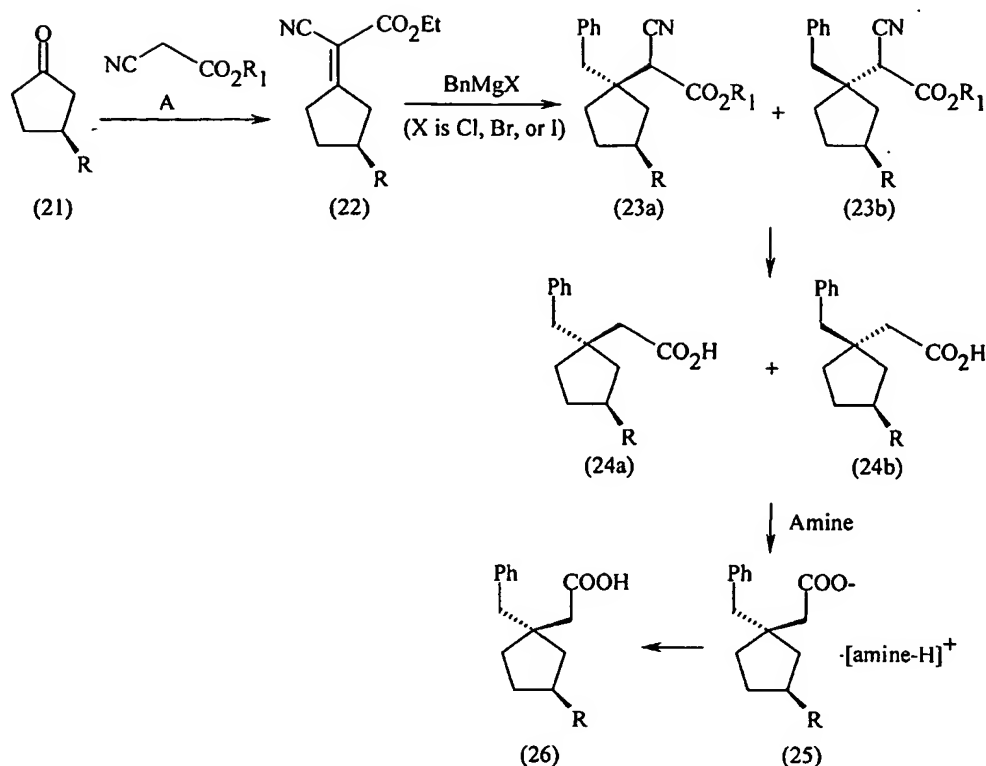
- e) converting the product of Step d) to a carboxylic acid of formula (26)



This process is outlined in Scheme 8.

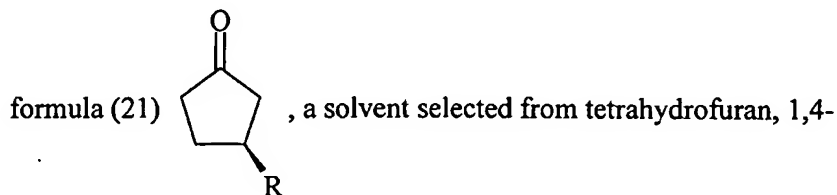
-90-

Scheme 8



Preferred is a process for the preparation of a compound of formula (26) wherein R is $\text{C}_1\text{-C}_{10}$ alkyl or $\text{C}_3\text{-C}_{10}$ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC-CH}_2\text{-CO}_2\text{R}_1$, wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl; *sec*-butyl, *tert*-butyl, and benzyl, to a mixture of a chiral cyclopentanone of



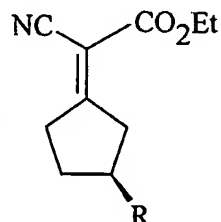
dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, *N,N*-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from

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β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl

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orthoformate to produce the alkene of formula (22)

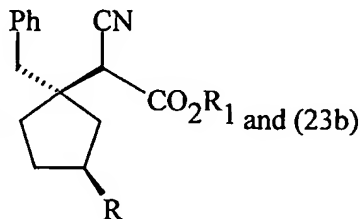


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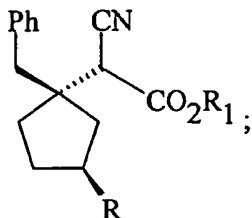
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition

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products of formulas (23a)

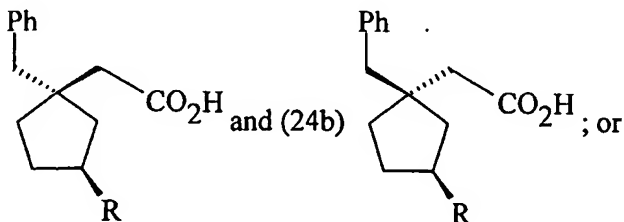


and (23b)



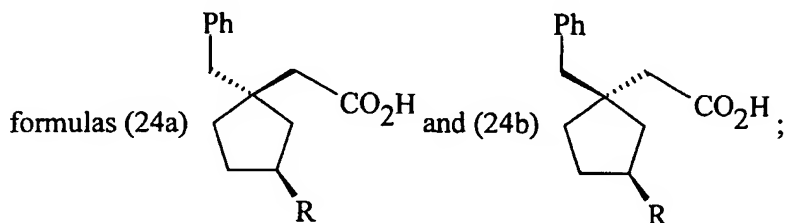
- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic acids of formulas (24a)

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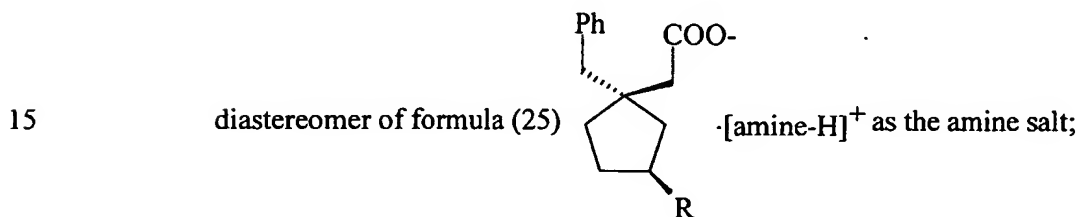


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adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the carboxylic acids of

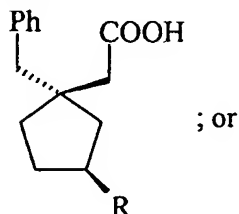


- 5 d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and
- 10 pyridine in a solvent selected from N,N-dimethylformamide, chloroform, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched



and

- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid
- 20 and water, and stirring to produce the carboxylic acid of formula (26)

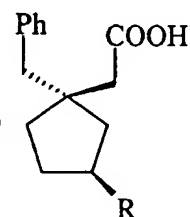


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partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic

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layer to produce the carboxylic acid of formula (26)

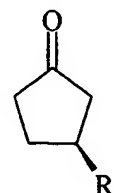


More preferred is a process for the preparation of a compound of formula (26) wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is

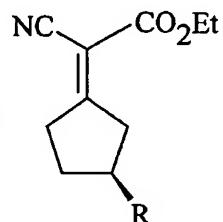
10

ethyl, to a mixture of a chiral cyclopentanone of formula (21)



toluene, acetic acid, and a Knoevenagel reaction catalyst which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark

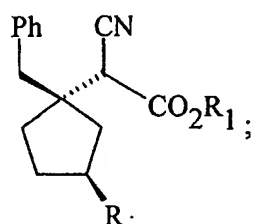
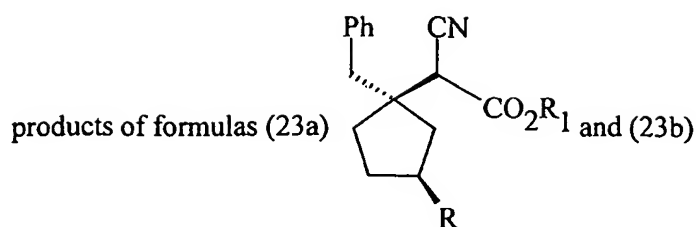
trap to produce the alkene of formula (22)



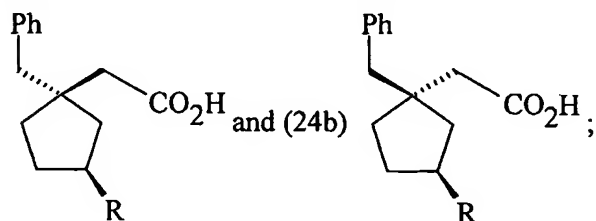
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition

15

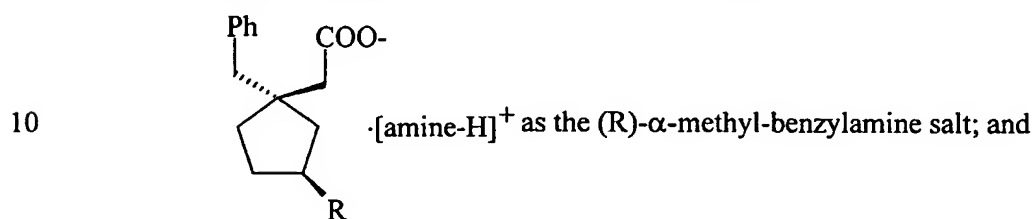
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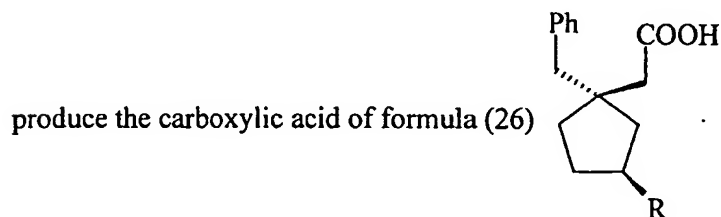
- 5 c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of formulas (24a)



- d) contacting the products of Step c) above with (R)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of formula (25)

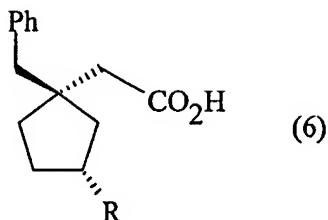


- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to



Further, the invention provides a key intermediate of formula (6)

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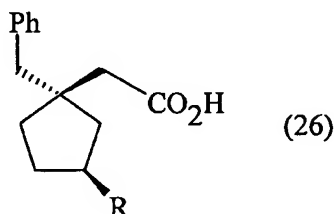
wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof.

5 Preferred is a compound of formula (6) and pharmaceutically acceptable salts thereof wherein R is C₁-C₁₀ alkyl.

More preferred is a compound of formula (6) and pharmaceutically acceptable salts thereof wherein R is selected from methyl, ethyl, and n-propyl.

Still more preferred is a compound of formula (6) named ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

10 Further, the invention provides a key intermediate of formula (26)



wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof.

15 Preferred is a compound of formula (26) and pharmaceutically acceptable salts thereof wherein R is C₁-C₁₀ alkyl.

More preferred is a compound of formula (26) and pharmaceutically acceptable salts thereof wherein R is selected from methyl, ethyl, and n-propyl.

Still more preferred is a compound of formula (26) named ((1R,3S)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

20 Further, the invention provides a compound of Formula I, wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of Formula I described above.

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Preferred is a compound of Formula I, wherein R is C₁-C₁₀ alkyl, prepared according to any one of the processes for the preparation of a compound of Formula I described above.

5 More preferred is a compound of Formula I, wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of Formula I described above.

Still more preferred is a compound of Formula I selected from:
((1R,3S)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid; and
((1R,3S)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride,
10 prepared according to any one of the processes for the preparation of a compound of Formula I described above.

Further, the invention provides a compound of Formula II, wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of Formula II described above.

15 Preferred is a compound of Formula II, wherein R is C₁-C₁₀ alkyl, prepared according to any one of the processes for the preparation of a compound of Formula II described above.

More preferred is a compound of Formula II, wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of Formula II described above.
20

Still more preferred is a compound of Formula II selected from:
((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid; and
((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride,
25 prepared according to any one of the processes for the preparation of a compound of Formula II described above.

Further, the invention provides a compound of Formula III, wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of Formula III described above.

Further, the invention provides a compound of Formula IV, wherein R is
30 as defined above, prepared according to any one of the processes for the preparation of a compound of Formula IV described above.

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Further, the invention provides a compound of formula (6), wherein R is as defined above, prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

Preferred is a compound of formula (6), wherein R is C₁-C₁₀ alkyl,
5 prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

More preferred is a compound of formula (6), wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

10 Still more preferred is a compound of formula (6) named
((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid, prepared according to any one of the processes for the preparation of a compound of formula (6) described above.

Further, the invention provides a compound of formula (26), wherein R is
15 as defined above, prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

Preferred is a compound of formula (26), wherein R is C₁-C₁₀ alkyl,
prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

20 More preferred is a compound of formula (26), wherein R is selected from methyl, ethyl, and *n*-propyl, prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

Still more preferred is a compound of formula (26) named
25 ((1R,3S)-1-benzyl-3-methyl-cyclopentyl)-acetic acid, prepared according to any one of the processes for the preparation of a compound of formula (26) described above.

Further, the invention provides a compound of Formula I selected from:
((1R,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid;
((1R,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;
30 ((1R,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid;
((1R,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;
((1R,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

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((1R,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

Further, the invention provides a compound of Formula II selected from:

((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid;

((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

5 ((1S,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

((1S,3R)-1-aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;

((1S,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

((1S,3R)-1-aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

Further, the invention provides compounds selected from:

10 E-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;

Z-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;

(R)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl
ester;

15 (S)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl
ester;

(R)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl
ester;

(S)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl
ester;

20 ((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene;

((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl
ester;

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic
acid;

25 ((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester;

(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl
ester;

30 [(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic
acid methyl ester;

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester;

[(1S,3R)-1-Carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl
ester;

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[(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid
tert-butyl ester;

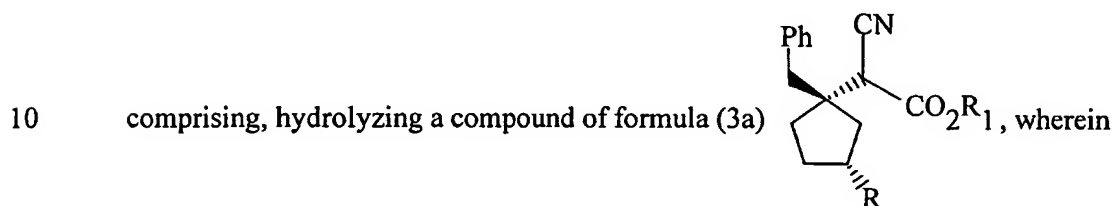
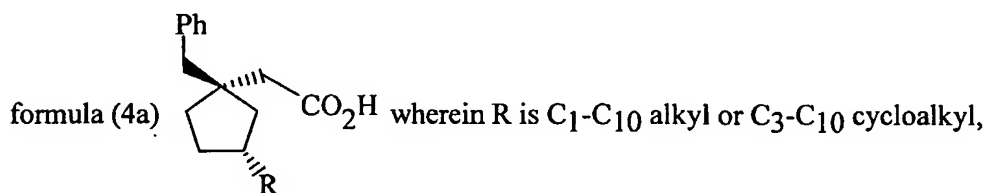
((1R,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl

5 ester; and

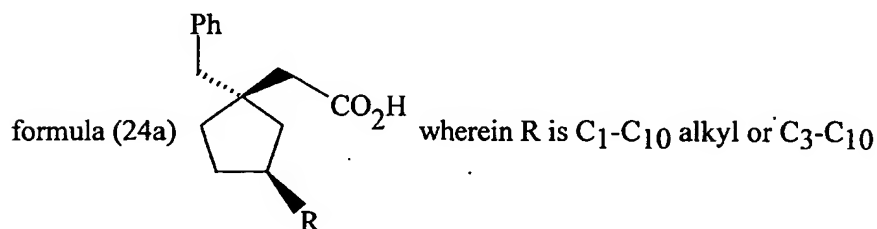
[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic
 acid methyl ester.

More preferred is a process for the preparation of a compound of

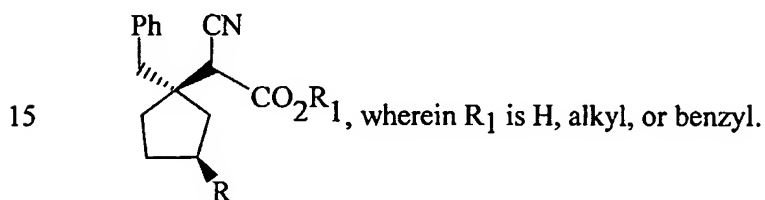


R₁ is H, alkyl, or benzyl.

More preferred is a process for the preparation of a compound of

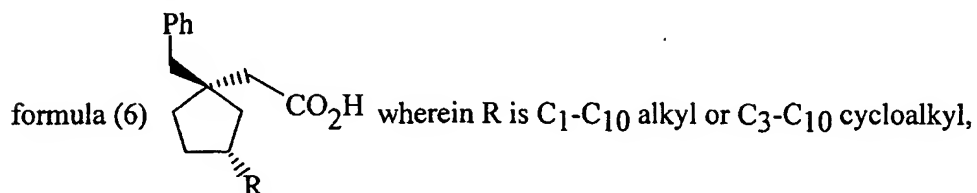


cycloalkyl, comprising, hydrolyzing a compound of formula (23a)

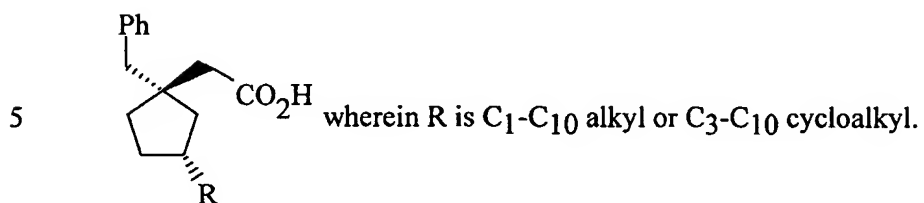
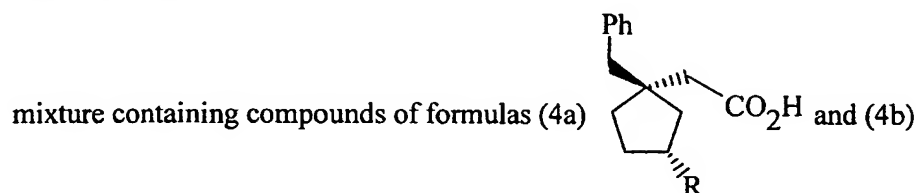


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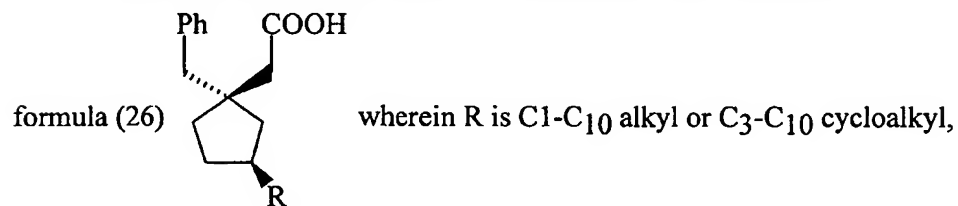
More preferred is a process for the preparation of a compound of



comprising, resolving a

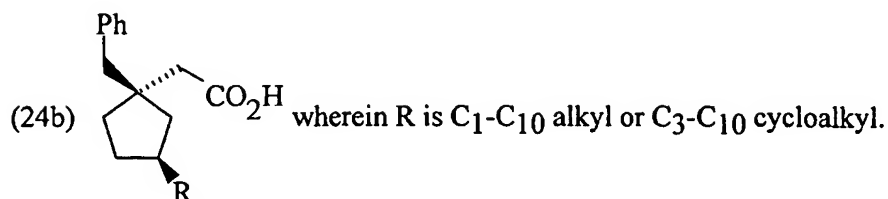
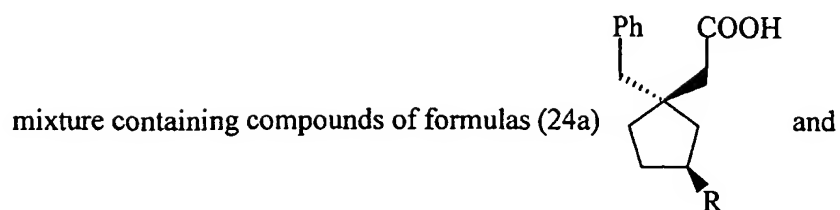


More preferred is a process for the preparation of a compound of

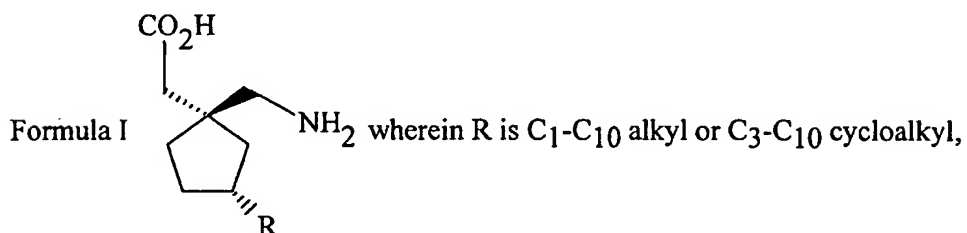


comprising, resolving a

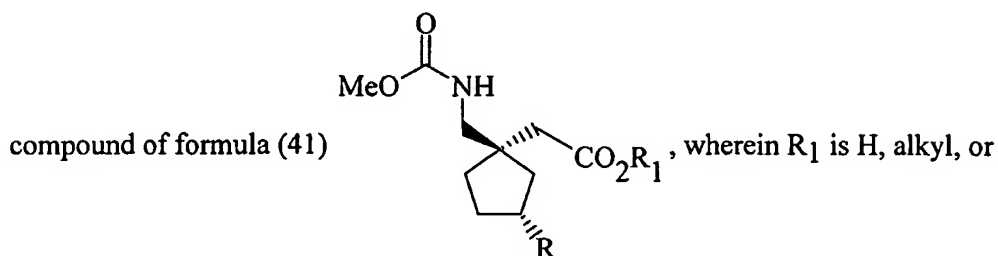
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More preferred is a process for the preparation of a compound of

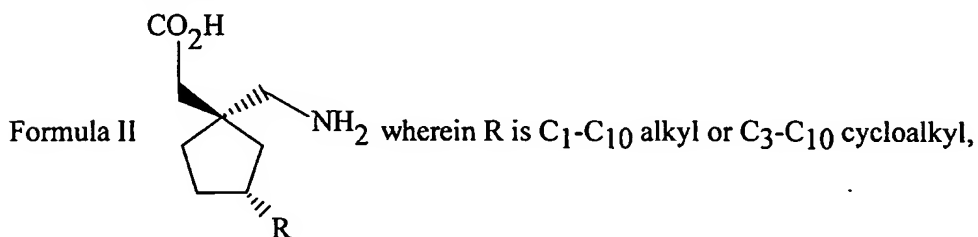


5 and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a



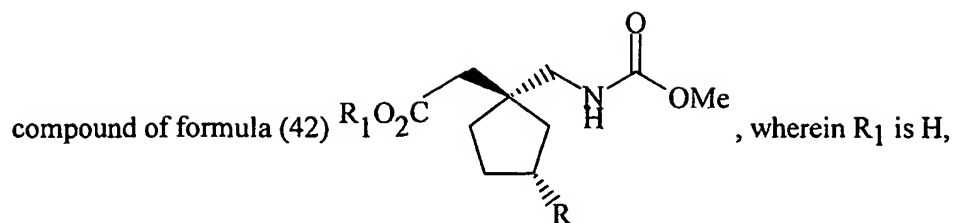
benzyl, and contacting the product, if desired, with an acid or a base.

More preferred is a process for the preparation of a compound of



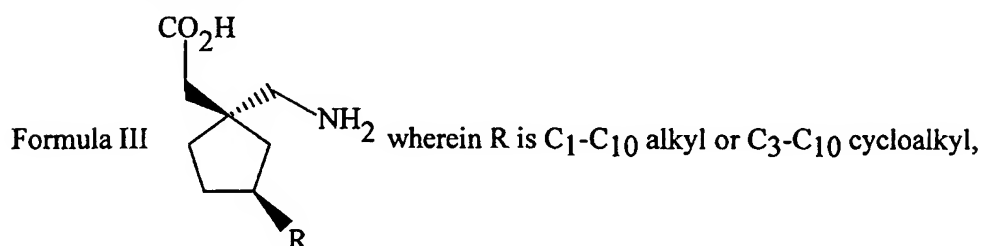
10 and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a

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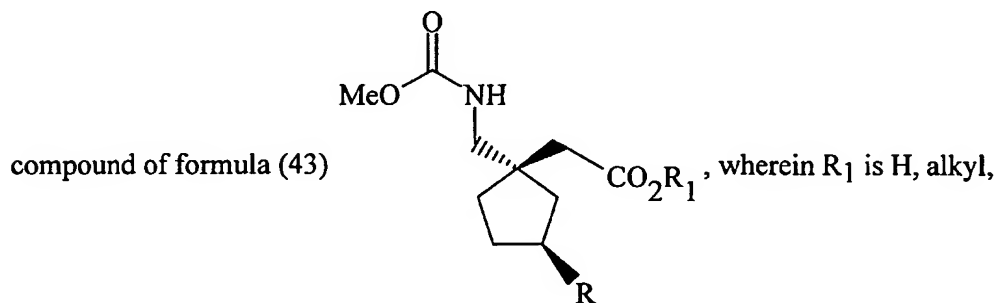


alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

More preferred is a process for the preparation of a compound of

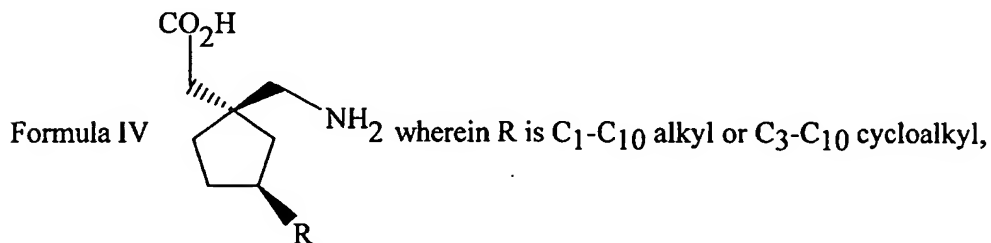


5 and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a



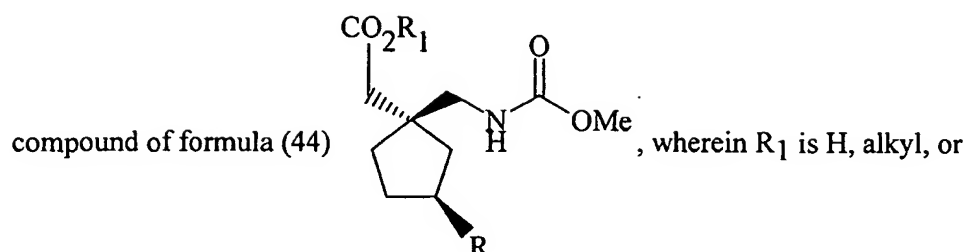
or benzyl, and contacting the product, if desired, with an acid or a base.

More preferred is a process for the preparation of a compound of



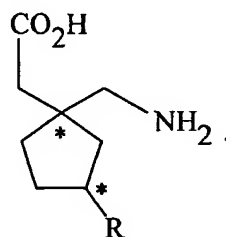
10 and pharmaceutically acceptable salt thereof, comprising, hydrolyzing a

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DETAILED DESCRIPTION OF THE INVENTION

The instant invention is an important process as it permits the synthesis of single isomers; it is a route to stereospecific 3-substituted 5-membered rings of formula



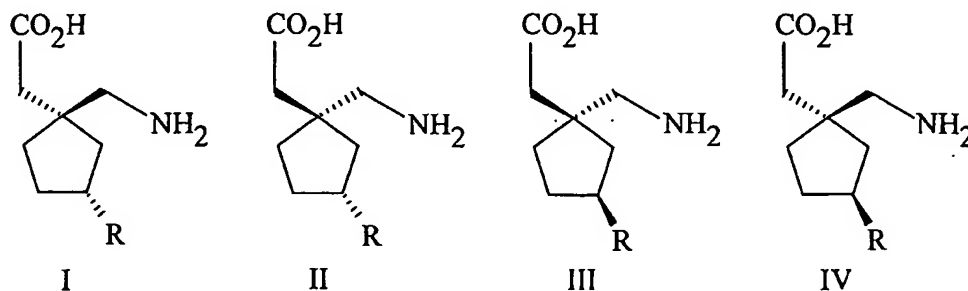
A key feature of the invention is the stereoselective preparation of a compound of formula (6) by selective fractional crystallization of a salt of formula (5) from a mixture of compounds of formulas (4a) and (4b), and conversion of a salt of formula (5) to a compound of formula (6). Another feature of the invention is the conversion of a compound of formula (2) to a mixture of compounds of formulas (3a) and (3b) wherein the yield of a compound of formula (3a) over a diastereomer of formula (3b) may be enhanced by optimizing certain reaction parameters such as, for example, temperature. Reaction of a compound of formula (2) at a relatively low temperature generally provides for a relatively higher yield of a compound of formula (3a) over (3b) than when the reaction is run at a higher temperature. The invention also provides for translation of the stereochemistry at the two chiral carbons of the cyclopentane ring of the resulting pure enantiomer of formula (6) into enantiomerically pure compounds of Formulas I or II with little or no racemization.

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Another key feature of the invention is the stereoselective preparation of a compound of formula (26) by selective fractional crystallization of salt of formula (25) from a mixture of compounds of formulas (24a) and (24b), and conversion of a salt of formula (25) to a compound of formula (26). Another feature of the invention is the conversion of a compound of formula (22) to a mixture of compounds of formulas (23a) and (23b) wherein the yield of a compound of formula (23a) over a diastereomer of formula (23b) may be enhanced by optimizing certain reaction parameters such as, for example, temperature. Reaction of a compound of formula (22) at a relatively low temperature generally provides for a relatively higher yield of a compound of formula (23a) over (23b) than when the reaction is run at a higher temperature. The invention also provides for translation of the stereochemistry at the two chiral carbons of the cyclopentane ring of the resulting pure enantiomer of formula (26) into enantiomerically pure compounds of Formulas III or IV with little or no racemization.

The final products are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammation especially arthritis, sleep disorders, premenstrual syndrome, and hot flashes.

The following experimental procedures provide a novel route to be used to stereoselectively synthesize 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof. These routes provide access to pure stereoisomers of Formulas I, II, III, and IV



wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl.

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Examples 1 and 3 below each show a synthesis of a compound of Formula II wherein R is methyl.

Example 2 below shows a synthesis of a compound of Formula I wherein R is methyl.

5 It is understood that compounds of Formulas I, II, III, or IV, or a pharmaceutically acceptable salt thereof, produced by a hydrolysis reaction such as, for example, step j) in the above process for the preparation of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or the process described above wherein a compound of formula (41) is hydrolyzed, may be formed as an
10 acid or base salt thereof, which salt may be optionally converted to a free amino acid form or a pharmaceutically acceptable salt form thereof by methods well known to a skilled person in the pharmaceutical or chemical arts.

The following terms are defined as used herein.

As used herein the term "C₁-C₁₀ alkyl" means a straight or branched alkyl
15 group or radical containing from 1 to 10 carbon atoms. Illustrative examples of C₁-C₁₀ alkyl include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 5-methyl-1-hexyl, 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-
20 1-heptyl, 5,5-dimethylhexyl, 1-nonyl, 2-nonyl, 1-decyl, and 2-decyl.

The term "C₃-C₁₀ cycloalkyl" means a cycloalkyl group or radical having from 3 to 10 carbon atoms. Illustrative examples of a C₃-C₁₀ cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl.

25 The term "stereoisomer" means any of a group of isomers in which identical atoms are linked in the same order but differ in their spatial arrangement.

* Asterisk symbol points out an enantiomerically enriched chiral carbon atom

30 AcOH Acetic acid
Alkali hydroxide LiOH, NaOH, KOH, or CsOH

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	NH ₄ OAc	Ammonium acetate
	BnMgCl or PhCH ₂ MgCl	Benzylmagnesium chloride
	<i>t</i> -BuOH or <i>tert</i> -butyl alcohol	1,1-Dimethylethanol
	<i>t</i> Butyl	1,1-Dimethylethyl
5	CH ₂ Cl ₂	Dichloromethane
	CCl ₄	Carbon tetrachloride
	CDCl ₃	Deuteriochloroform
	(CH ₃) ₃ SiCHN ₂	Trimethylsilyldiazomethane
	CN	Carbon-nitrogen triple bond (nitrile)
10	(COCl) ₂	Oxalyl chloride
	CsOH	Cesium hydroxide
	de	Diastereomeric excess
	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
	DMF	N,N-Dimethylformamide
15	DMSO	Dimethylsulfoxide
	DMSO- <i>d</i> ₆	Deuterated dimethylsulfoxide
	ee	Enantiomeric excess
	Et	Ethyl
	EtOAc	Ethyl acetate
20	Et ₃ N	Triethylamine
	HCl	Hydrogen chloride
	HCl (aq)	Hydrochloric acid
	6 <i>N</i> HCl	6 normal hydrochloric acid
	HCl (g)	Hydrogen chloride (gaseous)
25	¹ H-NMR	Proton (nuclear) magnetic resonance spectroscopy
	IR	Infrared spectroscopy
	<i>J</i>	Coupling constant in Hz
	KOH	Potassium hydroxide
30	LCMS	Liquid chromatography-mass spectrometry
	LiOH	Lithium hydroxide

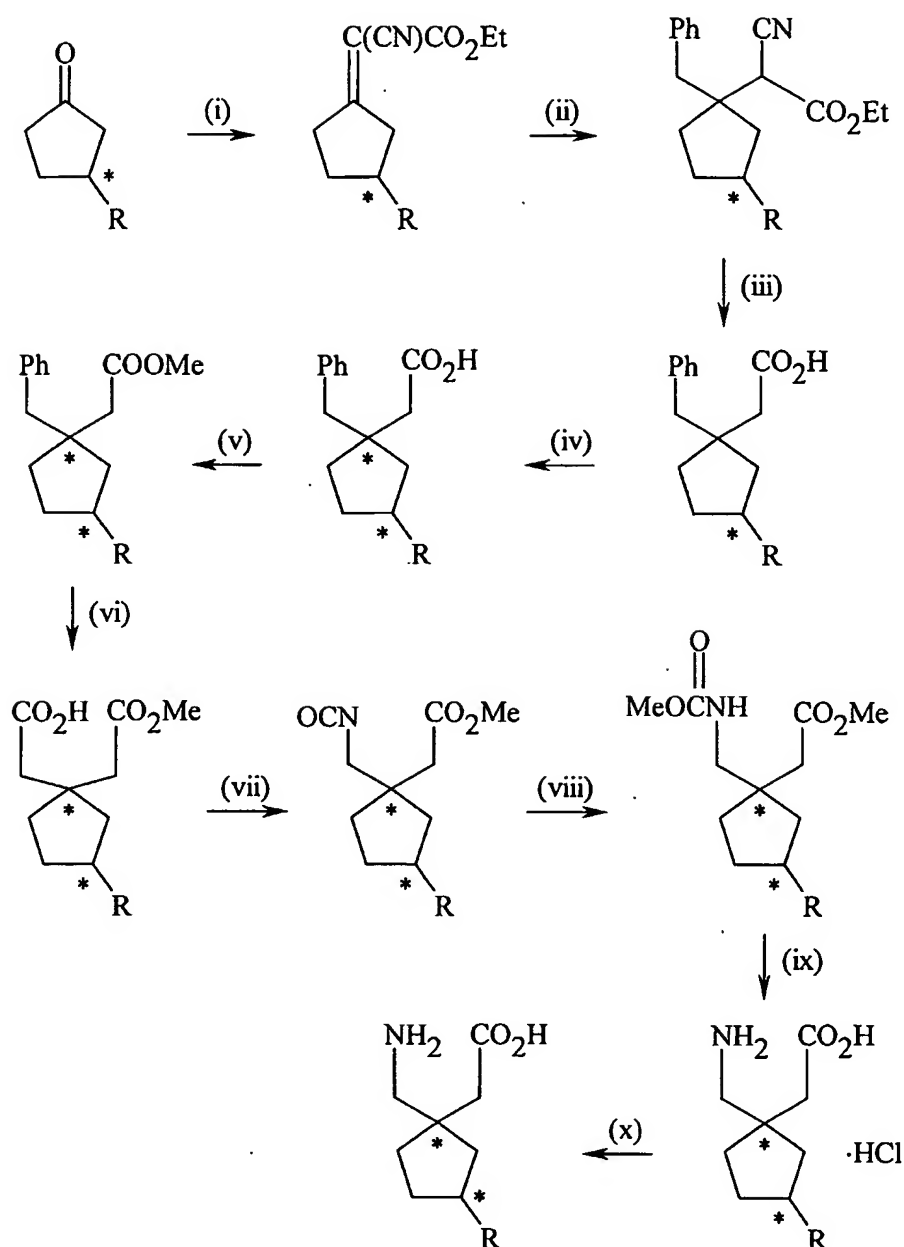
-107-

	Me	Methyl
	MeO	Methoxy
	MeCN	Acetonitrile
	MeI	Iodomethane
5	MeOH	Methanol
	MgSO ₄	Magnesium sulfate
	MS (ES ⁺)	Positive ion electrospray mass spectrometry
	MS (ES ⁻)	Negative ion electrospray mass spectrometry
	MS (CI ⁺)	Positive ion chemical ionization mass
10		spectrometry
	MS (CI ⁻)	Negative ion chemical ionization mass
		spectrometry
	<i>m/z</i>	mass per unit charge
	NCCH ₂ CO ₂ Et	Ethyl cyanoacetate
15	NaIO ₄	Sodium periodate
	NaOH	Sodium hydroxide
	ODS	Octadecyl-functionalized silica gel
	Ph	Phenyl
	(<i>i</i> -Pr) ₂ NEt	Diisopropylethylamine
20	R _f	R _f value
	RuCl ₃	Ruthenium(III) chloride
	SOCl ₂	Thionyl chloride
	TFA or CF ₃ CO ₂ H	Trifluoroacetic acid
	THF	Tetrahydrofuran

25

General Route A

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Reagents and Conditions:

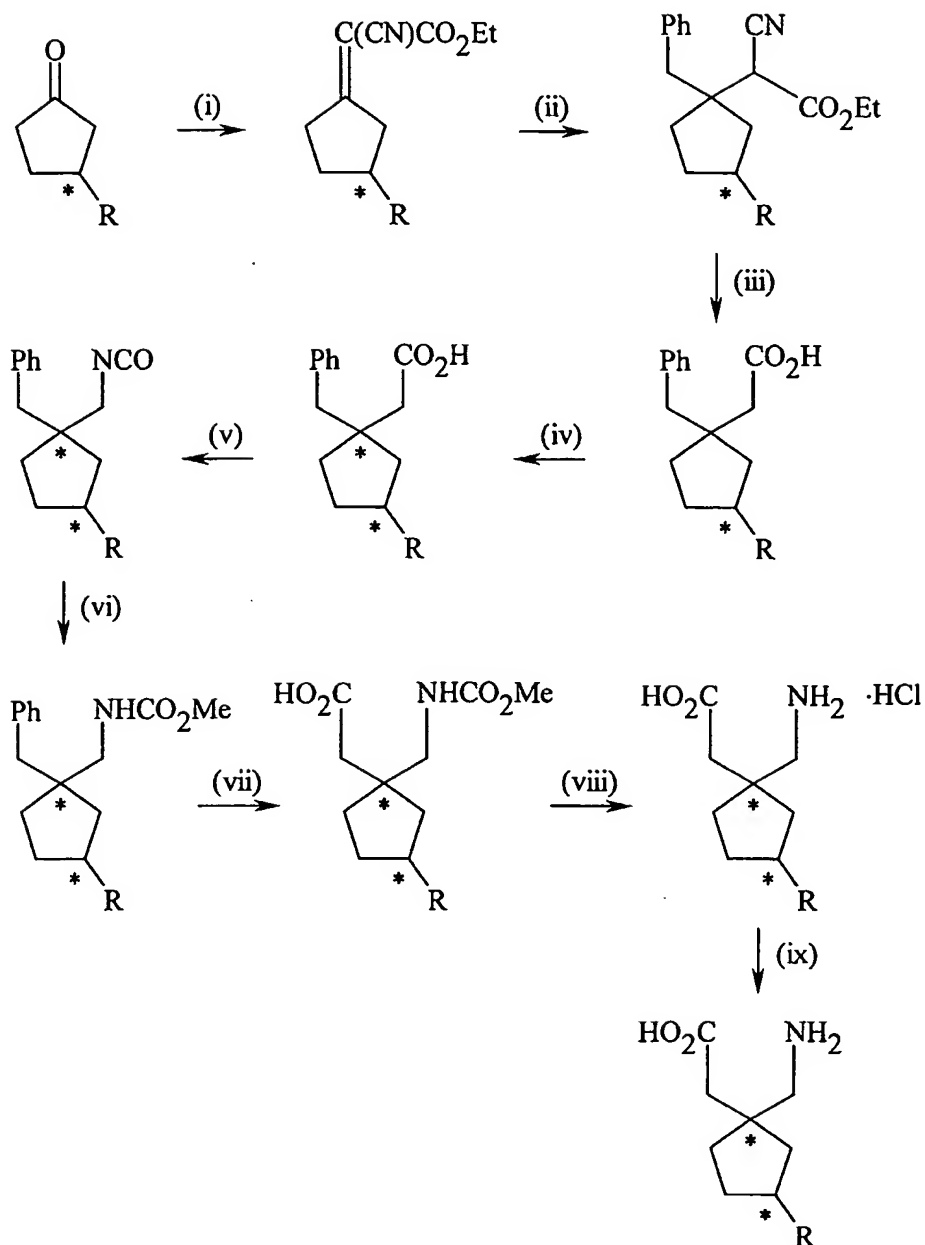
- (i) $\text{NCCH}_2\text{CO}_2\text{Et}$, catalyst (e.g., NH_4OAc , ACOH);
- (ii) BnMgCl ;
- 5 (iii) hydrolysis using, for example, alkali hydroxide (e.g., KOH);
- (iv) a) resolution using a resolving agent (e.g., (R)- or (S)- α -methylbenzylamine);
- b) conversion of the enriched stereoisomer to the free acid using, for example, hydrochloric acid;

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- (v) esterification using, for example, MeI and DBU;
- (vi) oxidation using, for example, RuCl_3 and NaIO_4 ;
- (vii) $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ and a base (e.g., Et_3N);
- (viii) MeOH;
- 5 (ix) hydrolysis using HCl (aq);
- (x) conversion to the free amino acid using, for example, H_2O and alkali hydroxide (e.g., NaOH).

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General Route B



Reagents and Conditions:

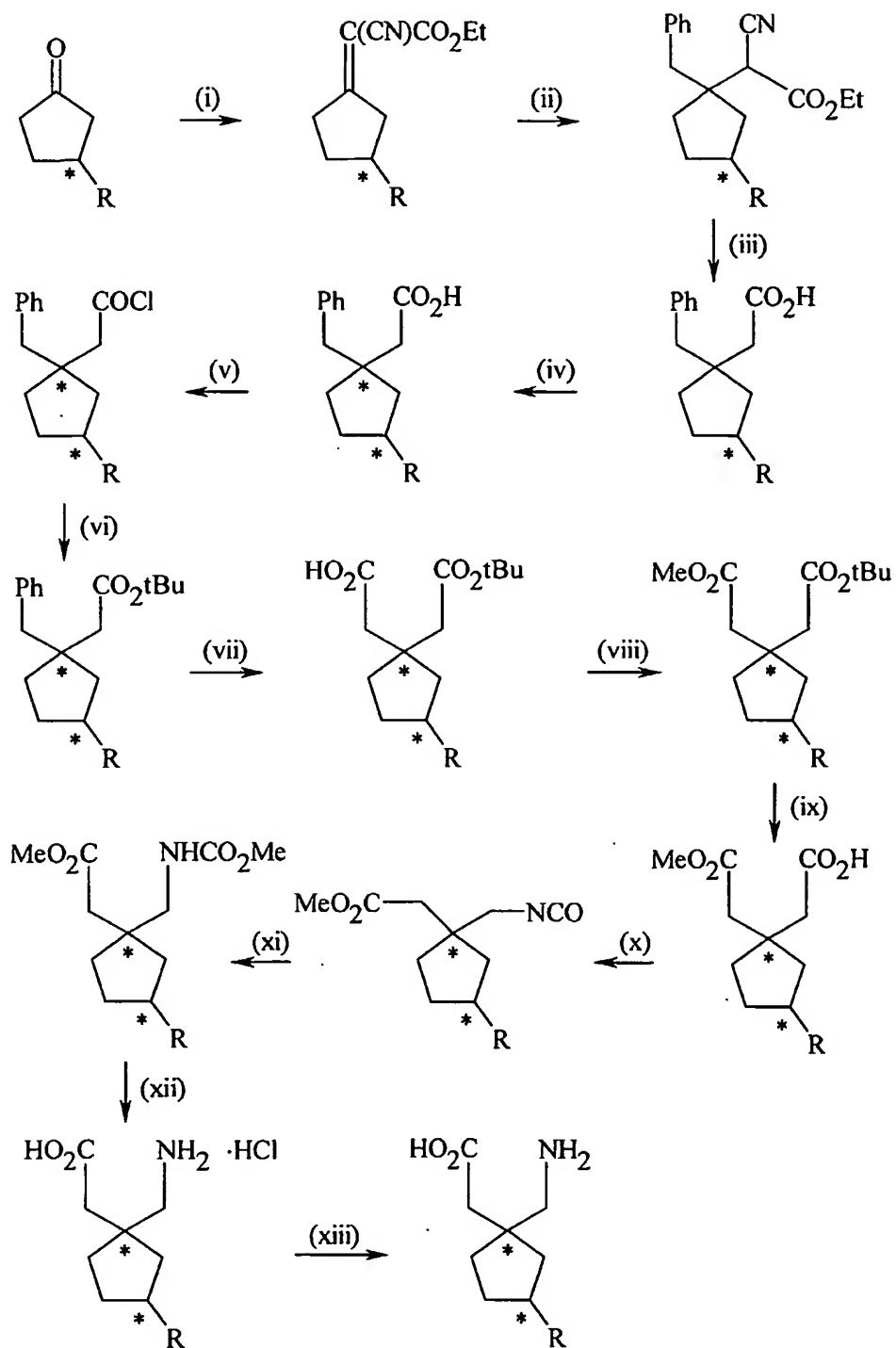
- 5 (i) $\text{NCCH}_2\text{CO}_2\text{Et}$, catalyst (e.g., NH_4OAc , AcOH);
 (ii) BnMgCl ;
 (iii) hydrolysis using, for example, alkali hydroxide (e.g., KOH);

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- (iv) a) resolution using a resolving agent (e.g., (R)- or (S)- α -methylbenzylamine);
b) conversion of salt of enriched stereoisomer to the free acid using, for example, hydrochloric acid;
- 5 (v) $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ and base (e.g., Et_3N);
(vi) MeOH ;
- (vii) oxidation using, for example, RuCl_3 and NaIO_4 ;
- (viii) hydrolysis using HCl (aq);
- (ix) conversion to the free amino acid using, for example, H_2O and alkali
10 hydroxide (e.g., NaOH).

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General Route C



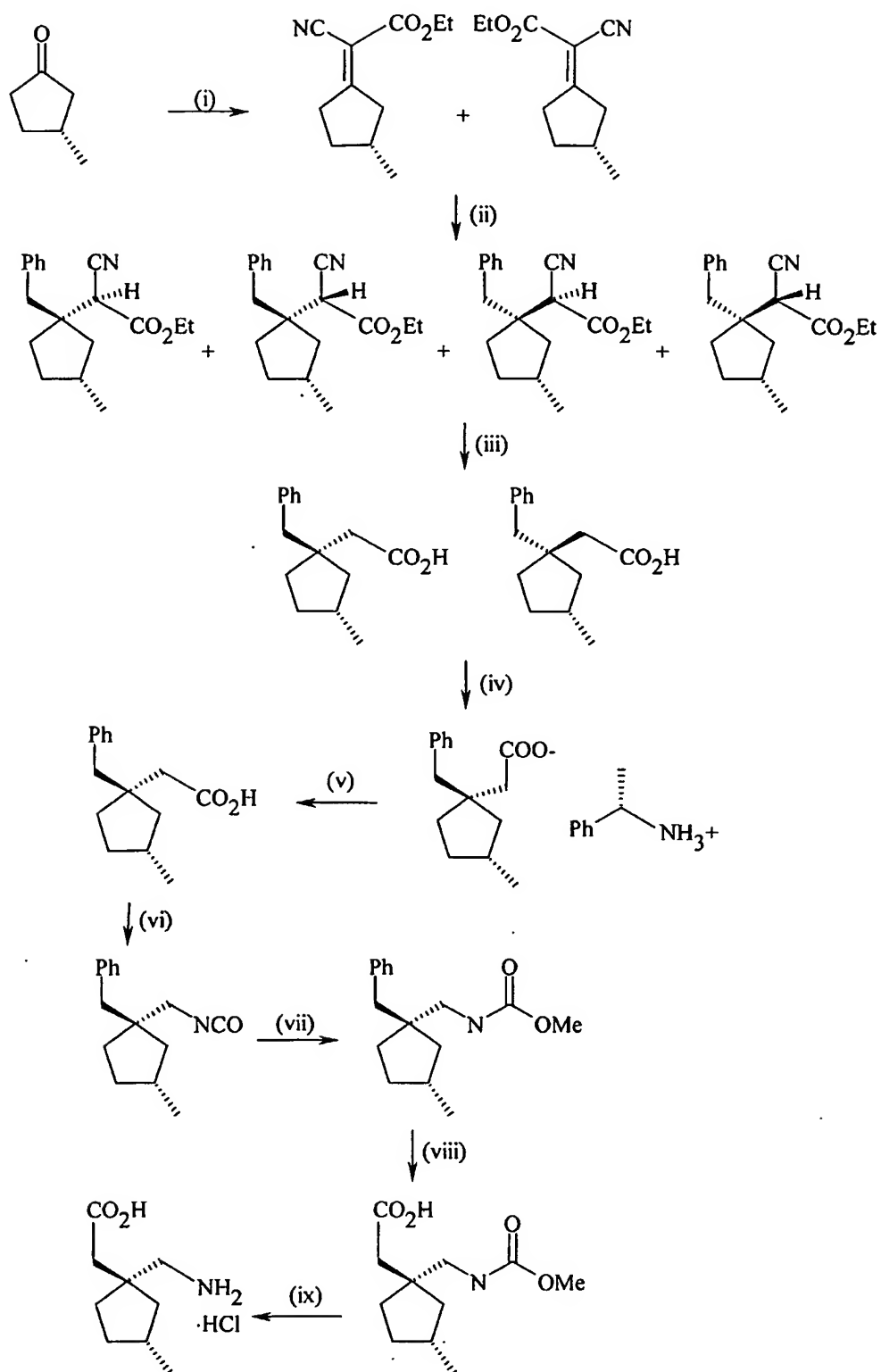
Reagents and Conditions:

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- (i) $\text{NCCH}_2\text{CO}_2\text{Et}$, catalyst (e.g., NH_4OAc , ACOH);
- (ii) BnMgCl ;
- (iii) hydrolysis using, for example, alkali hydroxide (e.g., KOH);
- (iv) a) resolution using a resolving agent (e.g., (R)- or (S)- α -methylbenzylamine);
5 b) conversion of salt of enriched stereoisomer to the free acid using, for example, hydrochloric acid;
- (v) chlorination using, for example, $(\text{COCl})_2$ or SOCl_2 ;
- (vi) tBuOH and base (e.g., Et_3N);
- 10 (vii) oxidation using, for example, RuCl_3 and NaIO_4 ;
- (viii) esterification using, for example, $(\text{CH}_3)_3\text{SiCHN}_2$ and MeOH ;
- (ix) dealkylation using, for example, $\text{CF}_3\text{CO}_2\text{H}$;
- (x) $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$ and a base (e.g., Et_3N);
- (xi) MeOH ;
- 15 (xii) hydrolysis using HCl (aq);
- (xiii) conversion to the free amino acid using, for example, H_2O and alkali hydroxide (e.g., NaOH).

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EXAMPLE 1



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- (i) $\text{NCCH}_2\text{CO}_2\text{Et}$, NH_4OAc , AcOH , toluene, reflux;
(ii) PhCH_2MgCl , THF, -78°C ;
(iii) KOH , ethylene glycol, 160°C ;
(iv) (S)-(-)- α -methyl benzylamine, EtOAc , 0°C ;
5 (v) HCl (aq);
(vi) $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$, Et_3N , toluene, reflux;
(vii) MeOH , toluene, reflux;
(viii) RuCl_3 , NaIO_4 , CCl_4 , MeCN , H_2O ;
(ix) 6*N* HCl , 1,4-dioxane.

10 (E and Z)-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester

(R)-(+)-3-Methylcyclopentanone (5 g, 51.0 mmol), ethyl cyanoacetate (5.42 mL, 51.0 mmol), ammonium acetate (0.4 g, 5.1 mmol), and glacial acetic acid (0.58 mL, 10.2 mmol) were refluxed in toluene (30 mL) using a Dean-Stark trap. After 6 hours, the mixture was allowed to cool and diluted with ethyl acetate
15 (100 mL), washed with water (3×80 mL), brine, and dried (MgSO_4). The solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel, heptane/ethyl acetate, 9:1) to give 8.87 g (90%) of a 1:1 mixture of (E and Z)-cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;
 R_f (heptane-ethyl acetate, 9:1) 0.28;

20 IR thin film(cm^{-1}) 2225 (CN), 1724 (C=O), 1617 (C=C);
 $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 4.27 (2H, q, J 7.2, $\text{CO}_2\text{CH}_2\text{Me}$), 4.26 (2H, q, J 7.2, $\text{CO}_2\text{CH}_2\text{Me}$), 3.35 (1H, dt, J 7.1, 1.6), 3.30 (1H, dt, J 7.1, 1.6), 3.23 (1H, ddd, J 8.1, 3.5, 1.7), 3.18 (1H, ddd, J 8.1, 3.4, 1.7), 3.05-2.67 (4H, m), 2.50-2.32 (2H, m), 2.29-1.96 (4H, m), 1.50-1.35 (2H, m), 1.34 (3H, t, J 7.2, $\text{CO}_2\text{CH}_2\text{Me}$), 1.33 (3H, t, J 7.1, $\text{CO}_2\text{CH}_2\text{Me}$), 1.10 (3H, d, J 6.6, Me), 1.08 (3H, d, J 6.6, Me);
25 MS (ES^-): m/z 192 (M-H, 100%).

(R and S)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester
and (R and S)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl
30 ester

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A mixture of (E and Z)-cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester (4.13 g, 21.4 mmol) in THF (30 mL) was added over 1 hour to a stirring solution of benzylmagnesium chloride (27.7 mL of a 1 M solution in ether, 27.7 mmol) in THF (50 mL) at -78°C under argon. After stirring for a further
5 1 hour, the mixture was quenched by addition of saturated ammonium chloride solution (15 mL). The mixture was allowed to warm to room temperature, diluted with ether (30 mL), and dilute hydrochloric acid (20 mL) was added. The organic layer was separated, and the aqueous layer was further extracted with ether (2 × 40 mL). The combined ether layers were washed with brine, dried (MgSO₄), and
10 the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel, heptane-ethyl acetate, 95:5) to give 5.8 g (100%) of a 7:7:3:3 mixture of diastereomeric (R and S)-((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester and (R and S)-((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester;
15 R_f (heptane-ethyl acetate, 9:1) 0.32;
IR thin film (cm⁻¹) 2246 (CN), 1740 (C=O), 1603 (C=C);
MS (ES⁻) *m/z* 284 (M-H, 100%).

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid and ((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid

20 The mixture of (R and S)-((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester and (R and S)-((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-cyano-acetic acid ethyl ester (1 g, 3.5 mmol) and potassium hydroxide (1.2 g, 21.4 mmol) were heated to 160°C in ethylene glycol (5 mL) for 16 hours. After this time, the mixture was allowed to cool and dilute hydrochloric acid (150 mL)
25 was added carefully. The mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic fractions were washed with brine, dried (MgSO₄), and the solvent was evaporated under reduced pressure. The residue was chromatographed (silica gel, heptane/ethyl acetate, 98:2) to give 0.65 g (80%) of a 7:3 mixture of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid and ((1R,3R)-
30 1-benzyl-3-methyl-cyclopentyl)-acetic acid as an oil;

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R_f (heptane-ethyl acetate, 98:2) 0.36;

IR thin film (cm^{-1}) 1702 (C=O);

^1H -NMR (400 MHz; CDCl_3) major isomer ((1S,3R)-1-benzyl-3-methyl-

cyclopentyl)-acetic acid: δ 7.31-7.21 (5H, m, Ph), 2.82 (1H, d, J 13.4,

5 $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2\text{H}$), 2.76 (1H, d, J 13.4, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2\text{H}$), 2.33 (2H, br s, CH_2Ph),
2.19-1.66 (m), 1.62-1.52 (m), 1.11 (1H, dd, J 13.0, 9.9), 1.01 (3H, d, J 6.6, Me);

minor isomer ((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid: δ

7.31-7.21 (5H, m, Ph), 2.89 (1H, d, J 13.2, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2\text{H}$), 2.84 (1H, d, J 13.4,

$\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2\text{H}$), 2.28 (2H, br s, CH_2Ph), 2.19-1.66 (m), 1.62-1.52 (m),

10 1.30-1.17 (m), 1.00 (3H, d, J 6.6, Me);

MS (CI^-): m/z 231 (M-H, 100%).

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid

(s)-(-)- α -Methyl benzylamine (8.8 g, 72.7 mmol) was added to a stirring solution of the diastereomeric mixture of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic

15 acid and ((1R,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (16.9 g,

72.7 mmol) dissolved in the minimum quantity of ethyl acetate. The mixture was placed in the fridge and left for 1 hour. After this time, the acid salt had

crystallised out and this was filtered off. The salt was recrystallized several times

from ethyl acetate (to 95% de). The salt was taken up in ethyl acetate, washed

20 with dilute hydrochloric acid, brine and dried (MgSO_4). The solvent was

evaporated under reduced pressure to give 6.8 g (40%) of ((1S,3R)-1-benzyl-

3-methyl-cyclopentyl)-acetic acid; LCMS (Prodigy® (Phenomenex, Ltd.) ODS

3 50 mm \times 4.6 mm id column, 5-50% Acetonitrile/water) Retention

Time = 2.01 min, 98% purity.

25 ((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene

Diphenylphosphoryl azide (4.48 g, 16 mmol), triethylamine (1.69 g, 16.8 mmol),

and acid ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (3.74 g, 16 mmol)

were refluxed in toluene (40 mL) for 17 hours. The mixture was allowed to cool

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and then taken up in ethyl acetate (150 mL), washed with saturated aqueous sodium hydrogen carbonate (200 mL), brine (150 mL), and dried (MgSO₄). The solvent was removed under reduced pressure to give 3.69 g (100%) of ((1S,3R)-1-isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene, which was used without further purification;

R_f (heptane-ethyl acetate, 8:2) 0.36;

IR thin film (cm⁻¹) 2262 (CN).

((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-benzene (3.69 g, 16 mmol) was refluxed in methanol (10 mL) and toluene (20 mL) for 16 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, heptane-ethyl acetate 9:1) to give 2.66 g (63%) of ((1S,3R)-1-benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester;

R_f (heptane-ethyl acetate, 8:2) 0.28;

IR thin film (cm⁻¹) 1709 (C=O);

¹H-NMR (400 MHz; CDCl₃) δ 7.32-7.16 (5H, m, Ph), 4.60 (1H, bs, NH), 3.68 (3H, s, OMe), 3.18-3.00 (2H, m, CH₂NH), 2.62-2.60 (2H, s, CH₂Ph), 0.99 (3H, d, *J* 6.8, Me), 2.05-1.92, 1.87-1.72, 1.60-1.40, 1.00-0.89 (7H, m);

MS (ES⁺) *m/z* 262 (M+H, 90%), 302 (M+CH₃CN+H, 100%);

LCMS (Prodigy® ODS 3 50 mm × 4.6 mm id column, 5-50% Acetonitrile (0.05% formic acid)/water (0.05% formic acid)) Retention Time = 2.11, 94% de.

[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid

((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid methyl ester (2.6 g, 9.9 mmol) and sodium periodate (29.8 g, 140 mmol) were stirred together in carbon tetrachloride (30 mL), acetonitrile (30 mL), and water for 6 hours. The mixture was cooled to 0°C, and ruthenium(III) chloride (0.04 g, 0.2 mmol) was added to the reaction mixture. The reaction was allowed to warm to room

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- temperature and stirred for 20 hours. Diethyl ether (50 mL) was added, and the mixture was then extracted with saturated aqueous sodium hydrogen carbonate (200 mL). The aqueous layer was acidified to pH 1 with 4N hydrochloric acid and re-extracted with ethyl acetate (200 mL), dried (MgSO₄), and the solvent was
- 5 evaporated under reduced pressure. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl acetate) to give 0.32 g (14%) of [(1S,3R)-1-(methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid;
- R_f (heptane-ethyl acetate, 8:2) 0.30;
- 10 IR thin film (cm⁻¹) 3338 (NH), 1712 (C=O);
- ¹H-NMR (400 MHz; CDCl₃): δ 9.29 (1H, s, COOH), 5.17 (1H, bs, NH), 3.71 (3H, s, OMe), 3.30 (1H, dd, *J* 14.4, 7.1, CH_AH_BNH₂), 3.17 (1H, dd, *J* 14.4, 6.6, CH_AH_BNH₂), 2.37 (2H, s, CH₂COOH), 2.20-1.00 (7H, m), 1.01 (3H, d, *J* 6.4, CHMe);
- 15 MS (ES⁺) *m/z* 230 (M+H, 63%), 481 (M+Na, 100%).

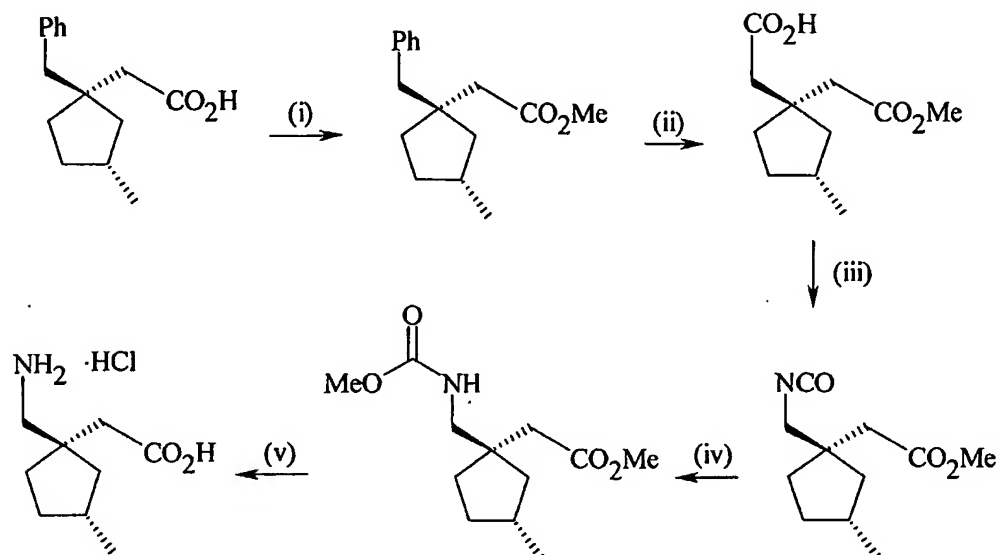
[(1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl]-acetic acid hydrochloride

- [(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid (0.32 g, 1.4 mmol) was refluxed in a mixture of 1,4-dioxane (3 mL) and 6N Hydrochloric acid (8 mL) for 4 hours. The mixture was allowed to cool, diluted
- 20 with water (200 mL), and washed with dichloromethane (2 × 200 mL). The aqueous layer was evaporated under reduced pressure, and the residue was recrystallized from ethyl acetate/methanol to give 0.17 g (59%) of [(1S,3R)-1-aminomethyl-3-methyl-cyclopentyl]-acetic acid hydrochloride;
- IR thin film (cm⁻¹) 1710 (C=O);
- 25 ¹H-NMR (400 MHz; DMSO-*d*₆): δ 2.96 (1H, d, *J* 12.8, CH_AH_BNH₂), 2.90 (1H, d, *J* 12.8, CH_AH_BNH₂), 2.40 (2H, s, CH₂COOH), 2.04 (1H, m, CHMe), 1.81-1.61, 1.51-1.43, 1.21-1.11 (5H, m), 1.06 (1H, dd, *J* 12.8, 10.4), 0.97 (3H, d, *J* 6.35, Me);
- MS (ES⁺) *m/z* 173 (M+H, 100%), 196 (M+Na, 10%);

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LCMS (Prodigy® ODS 3 50 mm × 4.6 mm id column, 5% for 2 min, 5-50% over 1.5 min of Acetonitrile (0.05% formic acid)/water (0.05% formic acid)) Retention Time = 0.92, 94% de.

EXAMPLE 2



- (i) $(\text{CH}_3)_3\text{SiCHN}_2$, MeOH, toluene;
(ii) RuCl_3 , NaIO_4 , CCl_4 , MeCN, H_2O ;
(iii) $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$, Et_3N , toluene, reflux;
(iv) MeOH, toluene, reflux;
(v) 6N HCl, 1,4-dioxane.

((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester

Trimethylsilyldiazomethane (31.5 mL of a 2 M solution in hexanes, 63 mmol) was added dropwise to a stirring solution of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (10 g, 43 mmol) in toluene (80 mL) and methanol (20 mL) at 0°C under argon, and the mixture was allowed to warm to room temperature. The mixture was stirred for 1 hour, and then the solvent was evaporated under reduced pressure. The residue was taken up in ethyl acetate (50 mL), washed with saturated sodium hydrogen carbonate solution, dilute hydrochloric acid, dried

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(MgSO₄), and the solvent removed *in vacuo* to give 10.6 g (100%) of ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester;

R_f (heptane-ethyl acetate, 9:1) 0.40;

IR thin film (cm⁻¹) 1736 (C=O);

5 ¹H-NMR (400 MHz; CDCl₃): δ 7.30-7.18 (5H, m, Ph), 3.69 (3H, s, OMe),
2.78 (1H, d, *J* 13.4, CH_AH_BCO₂Me), 2.72 (1H, d, *J* 13.4, CH_AH_BCO₂Me),
2.28 (2H, s, CH₂Ph), 2.16-1.50 (5H, m), 1.30-1.03 (2H, m), 1.00 (3H, d, *J* 6.6,
Me).

((1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid

10 ((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester (10.5 g,
43 mmol) and sodium periodate (128.0 g, 598 mmol) were stirred together in
carbon tetrachloride (120 mL), acetonitrile (120 mL), and water (210 mL) for
1 hour. The mixture was cooled to 10°C, and ruthenium(III) chloride (0.177 g,
0.86 mmol) was added to the reaction mixture. The reaction was allowed to warm
15 to room temperature and stirred for 20 hours. Diethyl ether (100 mL) was added,
and the mixture was acidified to pH 1 with concentrated hydrochloric acid and
then extracted with ether (2 × 200 mL). The organic layer was extracted with
saturated aqueous sodium hydrogen carbonate (2 × 200 mL) which was then
acidified to pH 1 with 4N hydrochloric acid and re-extracted with ethyl acetate,
20 dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by
chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl
acetate) to give 8.02 g (87.7%) of ((1S,3R)-1-methoxycarbonylmethyl-3-methyl-
cyclopentyl)-acetic acid;

R_f (heptane-ethyl acetate, 1:1) 0.46;

25 IR thin film (cm⁻¹) 3100 (OH), 1737 (C=O), 1705 (C=O);

¹H-NMR (400 MHz; CDCl₃): δ 3.68 (3H, s, OMe), 2.67-2.51 (4H, m), 2.06 (1H,
m), 1.97-1.79 (2H, m), 1.76-1.59 (2H, m), 1.29-1.08 (2H, m), 1.01 (3H, d, *J* 6.6,
Me);

MS (ES⁺) *m/z* 215 (M+H), 278 (M+Na, 100), 451 (2M+Na, 80%).

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((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester

Diphenylphosphoryl azide (8.07 mL, 37.4 mmol), triethylamine (5.36 mL, 39 mmol), and ((1S,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid (7.93 g, 37 mmol) were refluxed in toluene (80 mL) for 17 hours. The mixture was allowed to cool and then taken up in ethyl acetate (250 mL), washed with saturated aqueous sodium hydrogen carbonate (250 mL), brine (100 mL), and dried (MgSO₄). The solvent was removed under reduced pressure to give 7.82 g (100%) of ((1R,3R)-1-isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester which was used without further purification;

IR thin film (cm⁻¹) 2264 (CN), 1732 (C=O).

[(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester

((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester (7.82 g, 37 mmol) was refluxed in methanol (30 mL) and toluene (80 mL) for 17 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, heptane to heptane:ether 8:2) to give 2.60 g (29%) of [(1R,3R)-1-(methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester;

R_f (heptane-ethyl acetate, 1:1) 0.52;

IR thin film (cm⁻¹) 1728 (C=O), 1716 (C=O);

¹H-NMR (400 MHz; CDCl₃): δ 3.67 (6H, s, OMe, NHCO₂Me), 3.21 (1H, dd, J 7.08, 14.2, CH_AH_BNHCO₂Me), 3.11 (1H, dd, J 6.10, 13.9, CH_AH_BNHCO₂Me), 2.36 (2H, s, CH₂CO₂Me), 2.05 (1H, m, CHMe), 1.86-1.46 & 1.29-1.18 (5H, m), 0.99 (3H, d, J 6.59, Me).

((1R,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride

[(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester (2.60 g, 37 mmol) was refluxed in a mixture of 1,4-dioxane (15 mL)

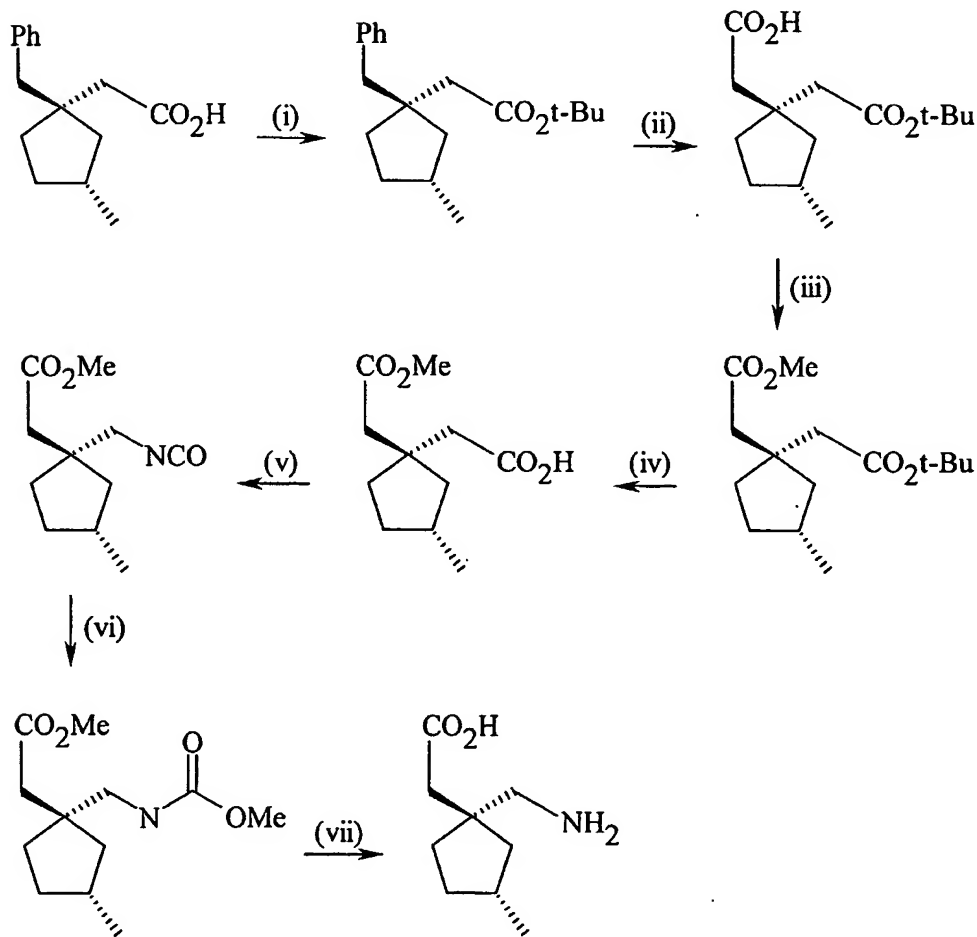
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and 6N Hydrochloric acid (30 mL) for 16 hours. The mixture was allowed to cool, diluted with water (80 mL), and washed with dichloromethane (2×200 mL). The aqueous layer was evaporated under reduced pressure, and the residue was recrystallized from ethyl acetate/methanol (95:5) to give 0.55 g (25%) of

IR thin film (cm^{-1}) 1724 ($\text{C}=\text{O}$);

^1H -NMR (400 MHz; $\text{DMSO}-d_6$): δ 2.92 (1H, d, J 12.9, $\text{CH}_\text{A}\text{H}_\text{BN}$), 2.87 (1H, d, J 12.9, $\text{CH}_\text{A}\text{H}_\text{BN}$), 2.45 (1H, d, J 15.9, $\text{CH}_\text{A}\text{H}_\text{B}\text{COOH}$), 2.40 (1H, d, J 15.9, $\text{CH}_\text{A}\text{H}_\text{B}\text{COOH}$), 1.95 (1H, m), 1.84-1.72 (2H, m), 1.60-1.48 (2H, m), 1.20 (1H, m), 1.04 (1H, m), 0.96 (3H, d, J 6.8, Me).

EXAMPLE 3



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- (i) a) oxalyl chloride, DMF, CH₂Cl₂; b) *t*-BuOH, (*i*-Pr)₂Net, CH₂Cl₂;
- (ii) RuCl₃, NaIO₄, CCl₄, MeCN, H₂O;
- (iii) (CH₃)₃SiCHN₂, MeOH, toluene;
- (iv) CF₃CO₂H, CH₂Cl₂;
- 5 (v) (PhO)₂P(O)N₃, Et₃N, toluene, reflux;
- (vi) MeOH, toluene, reflux;
- (vii) 6*N* HCl, 1,4-dioxane.

((1*S*,3*R*)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester

Oxalyl chloride (4.14 mL, 47 mmol) was added dropwise to a stirring solution of
 10 ((1*S*,3*R*)-1-benzyl-3-methyl-cyclopentyl)-acetic acid (10 g, 43 mmol) in
 dichloromethane under argon at room temperature. The reaction mixture was
 cooled to 5°C, dimethylformamide (1 mL) was carefully added, and the mixture
 was allowed to warm to room temperature and stirred for a further 2 hours. The
 solvent was removed *in vacuo* and the residue diluted with dichloromethane
 15 (60 mL). 1,1-Dimethylethanol (15 mL) was carefully added to the reaction
 mixture under argon followed by diisopropylethylamine (11.5 mL, 65 mmol). The
 mixture was stirred for 17 hours and then taken up in ethyl acetate, washed with
 saturated aqueous sodium hydrogen carbonate (2 × 200 mL), and dried (MgSO₄).
 The solvent was removed under reduced pressure, and the residue was purified by
 20 chromatography (silica gel, eluting with a gradient of heptane to 9:1 heptane:ethyl
 acetate) to give 10.92 g (88%) of ((1*S*,3*R*)-1-benzyl-3-methyl-cyclopentyl)-acetic
 acid *tert*-butyl ester;

R_f (heptane-ethyl acetate, 9:1) 0.64;

IR thin film (cm⁻¹) 1724 (C=O);

25 ¹H-NMR (400 MHz;CDCl₃): δ 7.29-7.17 (5H, m, Ph), 2.77 (1H, d, *J* 13.6,
 CH_AH_BPh), 2.71 (1H, d, *J* 13.6, CH_AH_BPh), 2.18 (1H, s, CH_AH_BCO₂^tButyl),
 2.17 (1H, s, CH_AH_BCO₂^tButyl), 1.49 (9H, s, CMe₃), 2.17-1.5 & 1.30-1.00 (7H,
 m), 1.00 (3H, d, *J* 6.8, CHMe).

[(1*S*,3*R*)-1-Carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester

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((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester (10.72 g, 37.2 mmol) and sodium periodate (124.77 g, 0.583 mol) were stirred together in carbon tetrachloride (120 mL), acetonitrile (120 mL), and water (210 mL) for 2 hours. The mixture was cooled to 0°C, and ruthenium(III) chloride (0.173 g, 0.83 mmol) was added to the reaction mixture. The reaction was allowed to warm to room temperature and stirred for 48 hours. Diethyl ether (60 mL) was added, and the mixture was then acidified to pH 2 by the addition of dilute hydrochloric acid. The mixture was extracted with ethyl acetate (2 × 200 mL), dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl acetate) to give 7.01 g (73.5%) of [(1S,3R)-1-carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

R_f (heptane-ethyl acetate, 1:1) 0.58;

IR thin film (cm⁻¹) 2953 (OH), 1726 (C=O) 1705 (C=O);

¹H-NMR (400 MHz; CDCl₃): δ 2.51 (2H, s, CH₂CO), 2.46 (2H, s, CH₂CO), 1.47 (9H, s, CMe₃), 2.05-2.15, 1.95-1.80, 1.75-1.60, 1.30-1.03 (7H, m), 1.01 (3H, d, *J* 6.4, Me).

[(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester

Trimethylsilyldiazomethane (14 mL of a 2 M solution in hexanes, 26.9 mmol) was added dropwise to a stirring solution of [(1S,3R)-1-carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester (6.9 g, 26.9 mmol) in toluene (60 mL) and methanol (15 mL) at 10°C under argon, and the mixture was allowed to warm to room temperature. The mixture was stirred for 2 hours, and then the solvent was evaporated under reduced pressure. The residue was taken up in ethyl acetate (200 mL), washed with saturated sodium hydrogen carbonate solution, dilute hydrochloric acid, dried (MgSO₄), and the solvent removed *in vacuo*. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 95:5 heptane:ethyl acetate) to give 6.73 g (92.4%) of [(1S,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

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R_f (heptane-ethyl acetate, 9:1) 0.36;

IR thin film (cm⁻¹) 1738 (C=O) 1732 (C=O);

¹H-NMR (400 MHz; CDCl₃): δ 3.65 (3H, s, OMe), 2.52 (2H, m, CH₂CO₂),

2.45 (1H, d, *J* 4.8, CH₂CO₂), 1.44 (9H, s, CMe₃), 2.05-1.5, 1.30-1.10 (7H, m),

5 1.00 (3H, d, *J* 6.8, Me).

[(1R,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid

[(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester (6.64 g, 24.6 mmol) and trifluoroacetic acid (10 mL) were stirred together in

dichloromethane (30 mL) for 17 hours at room temperature. The mixture was

10 carefully poured into aqueous sodium carbonate and extracted with ethyl acetate (200 mL). The aqueous was acidified to pH 1 with concentrated hydrochloric acid and re-extracted with ethyl acetate (3 × 200 mL), dried (MgSO₄), and

concentrated *in vacuo*. The residue was purified by chromatography (silica gel, eluting with a gradient of heptane to 1:1 heptane:ethyl acetate) to give 5.26 g

15 (100%) of [(1R,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid;

R_f (heptane-ethyl acetate, 1:1) 0.46;

IR thin film (cm⁻¹) 2952 (OH), 1737 (C=O), 1706(C=O);

¹H-NMR (400 MHz; CDCl₃): δ 3.68 (3H, s, OMe), 2.67 (1H, d, *J* 15.0,

CH_AH_BCO₂), 2.61 (1H, d, *J* 14.9, CH_AH_BCO₂), 2.58 (1H, d, *J* 14.8,

20 CH_AH_BCO₂), 2.53 (1H, d, *J* 14.8, CH_AH_BCO₂), 1.93-1.81, 1.75-1.59,

1.75-1.63 (6H, m), 1.16 (1H, dd, *J* 19.5, 9.3), 1.01 (3H, d, *J* 6.35, Me).

[(1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl]-acetic acid methyl ester

Diphenylphosphoryl azide (5.35 mL, 24.8 mmol), triethylamine (3.55 mL,

25.6 mmol), and [(1R,3R)-1-methoxycarbonylmethyl-3-methyl-cyclopentyl]-

25 acetic acid (5.26 g, 24.5 mmol) were refluxed in toluene (80 mL) for 17 hours.

The mixture was allowed to cool and then taken up in ethyl acetate (300 mL),

washed with saturated aqueous sodium hydrogen carbonate solution (250 mL),

brine (200 mL), and dried (MgSO₄). The solvent was removed under reduced

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pressure to give 5.19 g (100%) of ((1S,3R)-1-isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester which was used without further purification; IR thin film (cm^{-1}) 2262 (NCO), 1732 (C=O).

5 [(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester

((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester (5.19 g, 24.5 mmol) was refluxed in methanol (30 mL) and toluene (80 mL) for 17 hours and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, heptane-ethyl acetate 9:1) to give 4.62 g (77%) of [(1S,3R)-1-(methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester; R_f (heptane-ethyl acetate, 1:1) 0.59;

IR thin film (cm^{-1}) 1730 (C=O);

^1H -NMR (400 MHz; CDCl_3): δ 3.68 (6H, s, OMe, NHCO_2Me), 3.27 (1H, dd, J 13.7, 6.8, $\text{CH}_\text{A}\text{H}_\text{B}\text{NHCO}_2\text{Me}$), 3.13 (1H, dd, J 13.9, 6.4, $\text{CH}_\text{A}\text{H}_\text{B}\text{NHCO}_2\text{Me}$), 2.37 (1H, d, J 13.9, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2$), 2.33 (1H, d, J 13.9, $\text{CH}_\text{A}\text{H}_\text{B}\text{CO}_2$), 2.09-1.99 (1H, m, CHMe), 1.88-1.76, 1.69-1.43, 1.28-1.19 (6H, m), 1.01 (3H, d, J 6.4, Me); m/z (Cl^+) 244 ($\text{M}+\text{H}$, 100%).

20 [(1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl]-acetic acid hydrochloride

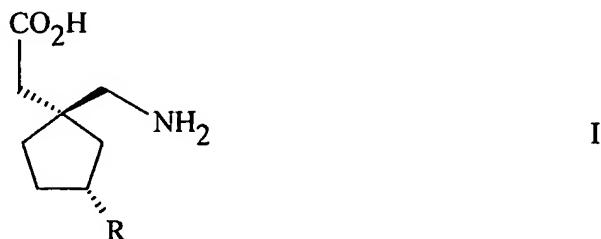
[(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester (2.84 g, 11.7 mmol) was refluxed in a mixture of 1,4-dioxane (15 mL) and 6N Hydrochloric acid (30 mL) for 17 hours. The mixture was allowed to cool, diluted with water (200 mL), and washed with dichloromethane (2×100 mL). The aqueous layer was evaporated under reduced pressure, and the residue was recrystallized from ethyl acetate/methanol (95:5) to give 1.28 g (53%) of ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride; IR thin film (cm^{-1}) 1710 (C=O);

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- $^1\text{H-NMR}$ (400 MHz; $\text{DMSO-}d_6$): δ 2.96 (1H, d, J 12.8, $\text{CH}_A\text{H}_B\text{NH}_2$), 2.90 (1H, d, J 12.8, $\text{CH}_A\text{H}_B\text{NH}_2$), 2.40 (2H, s, CH_2COOH), 2.09-1.98 (1H, m, CHMe), 1.81-1.61, 1.51-1.43, 1.21-1.11 (5H, m), 1.04 (1H, dd, J 13.2, 10.4), 0.97 (3H, d, J 6.35, Me);
- 5 MS (ES^+) m/z 173 ($\text{M}+\text{H}$, 100%), 196 ($\text{M}+\text{Na}$, 10%);
- LCMS (Prodigy® ODS 3 50 mm \times 4.6 mm id column, 5% for 2 min, 5-50% over 1.5 min of acetonitrile (0.05% formic acid)/water (0.05% formic acid)) Retention Time = 0.92, 94% de; (Found: C, 49.5; H, 8.78; N, 6.37.
- $\text{C}_9\text{H}_{17}\text{NO}_2$ 1HCl $0.6\text{H}_2\text{O}$ requires C, 49.5; H, 8.86; N, 6.41).

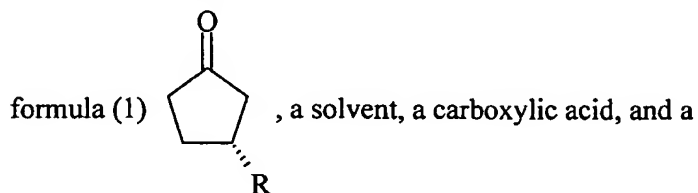
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CLAIMS

1. A process for the preparation of a compound of Formula I

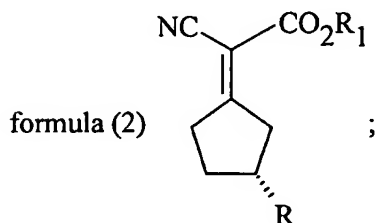


wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

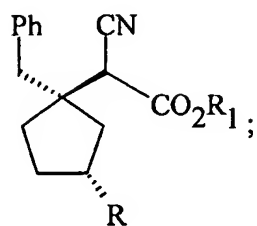
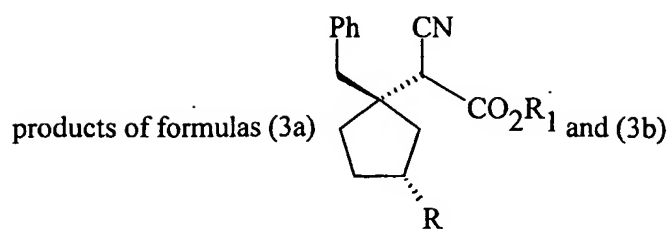


Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

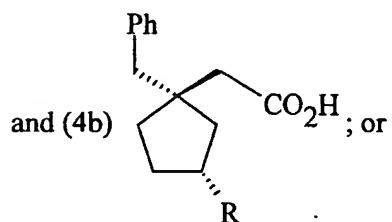
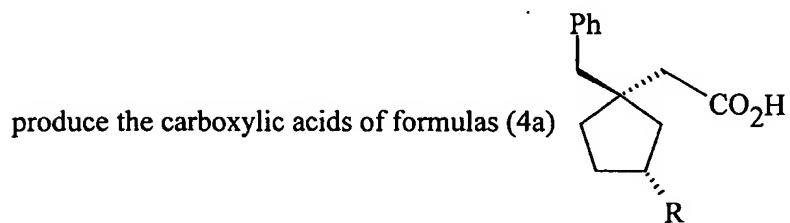


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

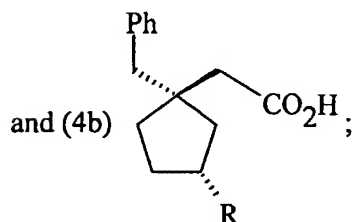
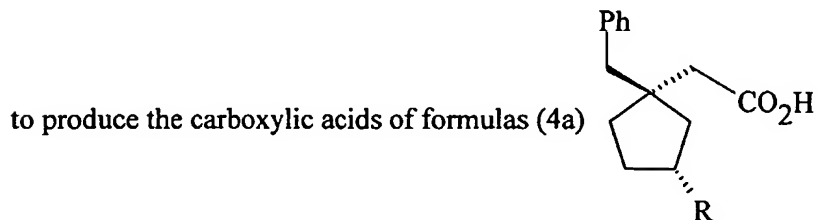
-130-



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, or cesium hydroxide in a solvent and stirring, and then acidifying to

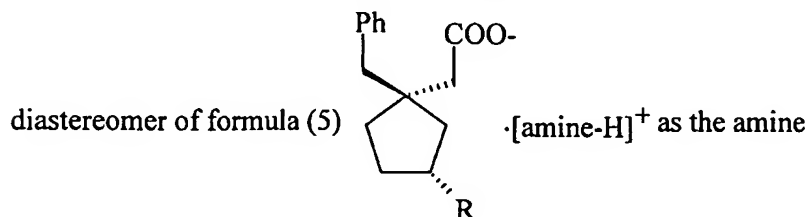


adding the products of Step b) above to an acid mixture and stirring



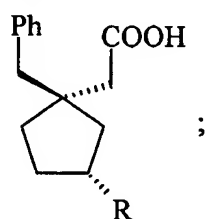
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- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

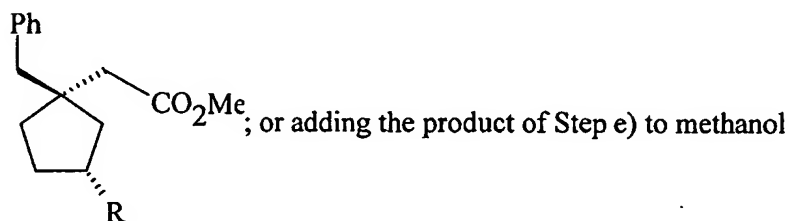


salt;

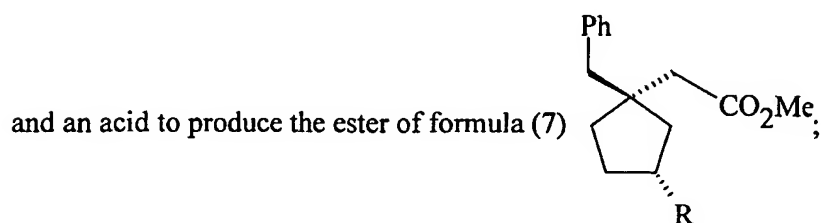
- 5 e) converting the product of Step d) to a carboxylic acid of formula (6)



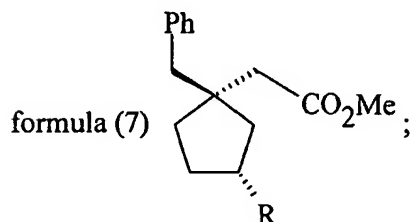
- f) adding the product of Step e) to a mixture of iodomethane, a solvent, and a base, and stirring to produce the ester of formula (7)



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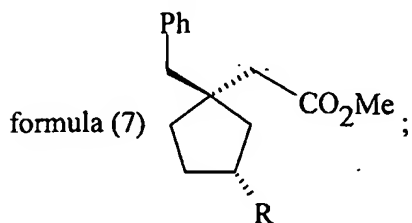


or adding the product of Step e) above to trimethylsilyldiazo-methane and methanol in a solvent to produce the ester of

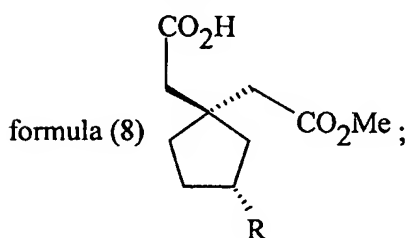


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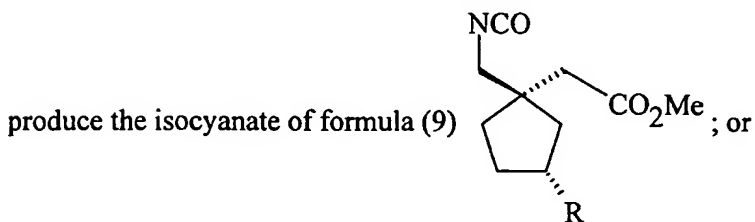
or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in a solvent to produce ester of



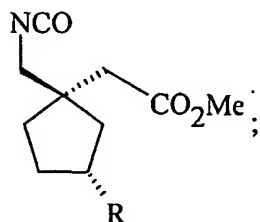
- g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of



- h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to

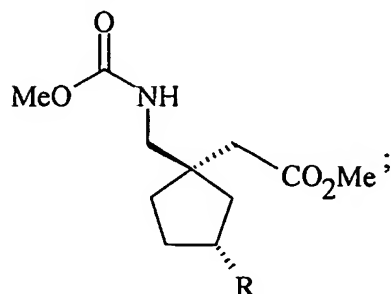


adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (9)



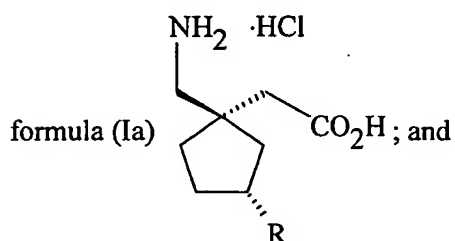
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- i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (10)

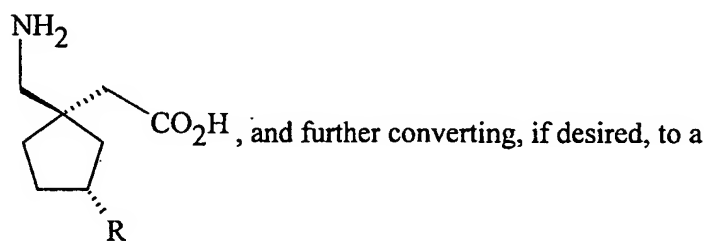


- j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of

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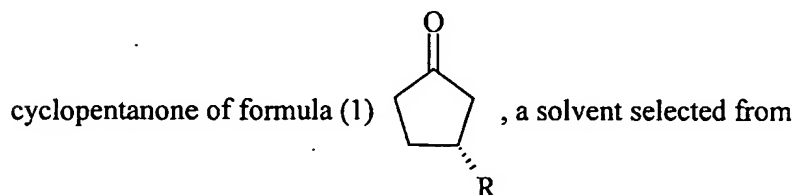
- k) converting the product of Step j) to a compound of formula (I)



pharmaceutically acceptable salt by known means.

- 10 2. A process according to Claim 1 which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral

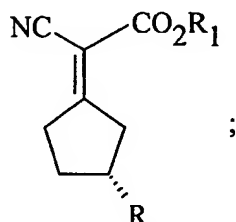


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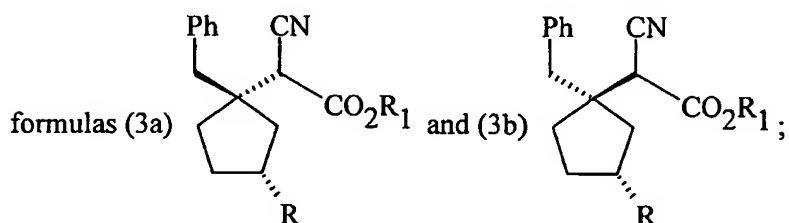
tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a

5 Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and

10 triethyl orthoformate to produce the alkene of formula (2)

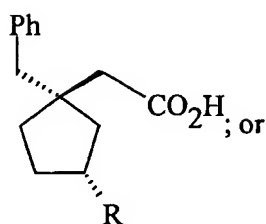
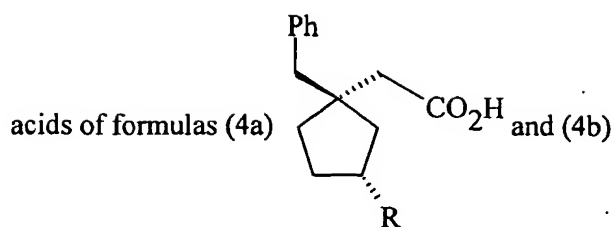


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or
- 15 benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of

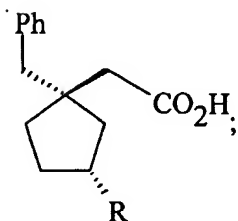
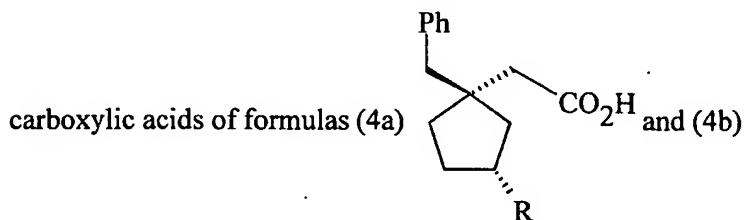


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic
- 20

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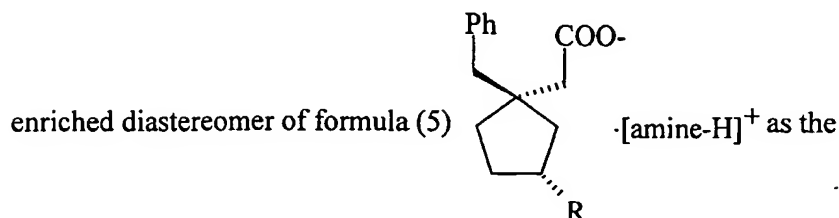
adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the



- d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and

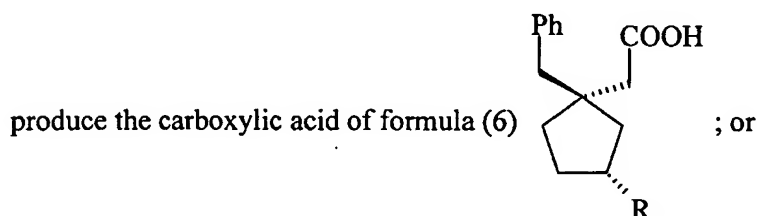
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1,4-dioxane, and recrystallizing the salt so formed to produce the

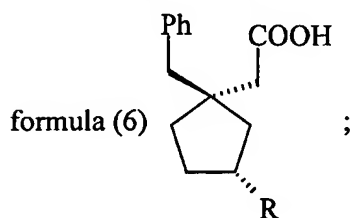


amine salt;

- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, or hydrochloric acid dissolved in acetic acid to which water is added and stirring to

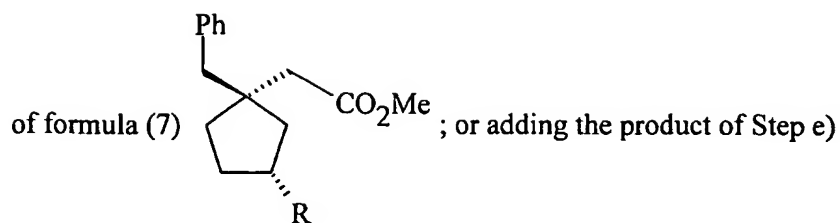


partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of

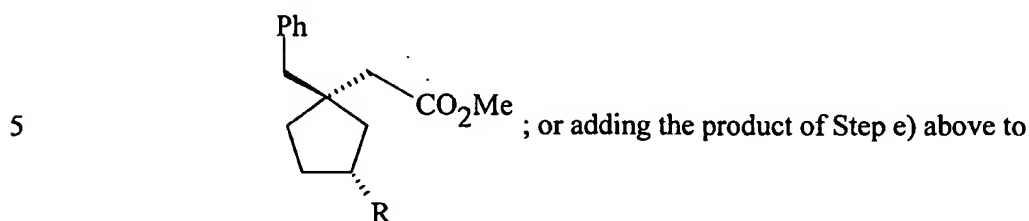


- f) adding the product of Step e) above to a mixture of iodomethane, a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene, and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and stirring at a temperature of from -40°C to 110°C to produce the ester

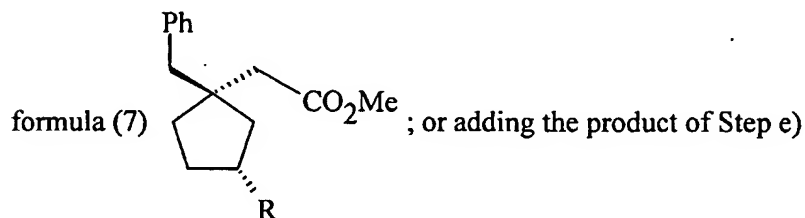
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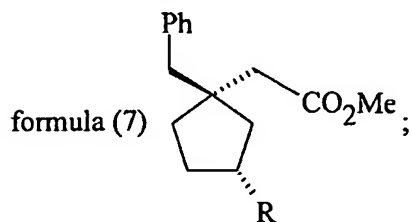
above to a mixture of methanol and concentrated sulphuric acid,
concentrated hydrochloric acid, or hydrogen chloride at a
temperature of from 0°C to 100°C to produce the ester of formula (7)



trimethylsilyldiazomethane and methanol in benzene or toluene at a
temperature of from -40°C to 100°C to produce the ester of



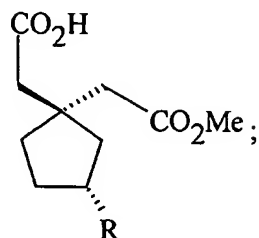
10 above to diazomethane or trimethylsilyldiazomethane in a solvent
selected from benzene, toluene, dichloromethane, and diethyl ether at
a temperature of from -40°C to 40°C to give a compound of



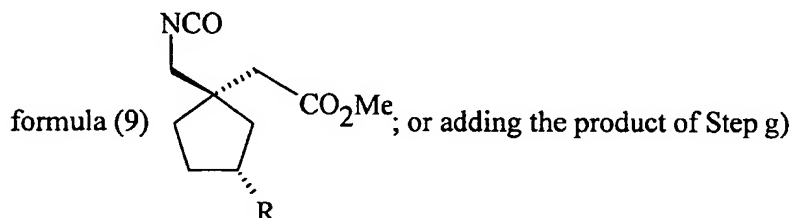
15 g) adding the product of Step f) to a mixture of carbon tetrachloride or
ethyl acetate, and acetonitrile, water, sodium periodate, and
ruthenium(III) chloride, and stirring at a temperature from -40°C to

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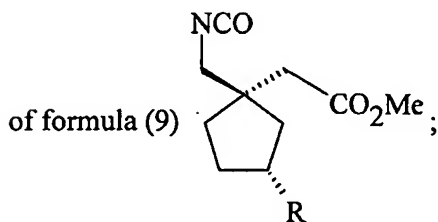
80°C to produce the carboxylic acid of formula (8)



- h) adding the product of Step g) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from 0°C to 150°C to produce the isocyanate of



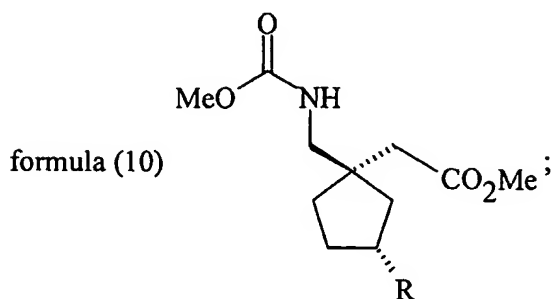
above to ethyl chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate



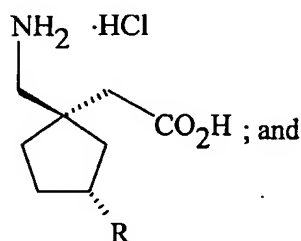
- i) adding the product of Step h) to a mixture of a solvent selected from toluene, benzene, xylenes and *n*-heptane, and methanol, and stirring

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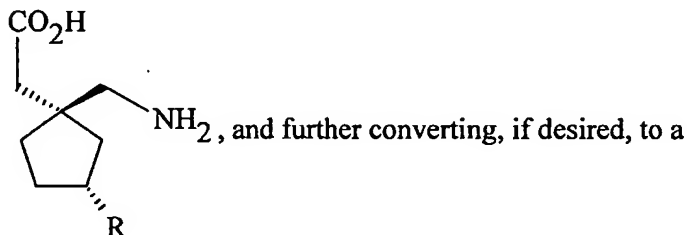
at a temperature from 0°C to 150°C to produce the carbamate of



- j) adding the product of Step i) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula Ia



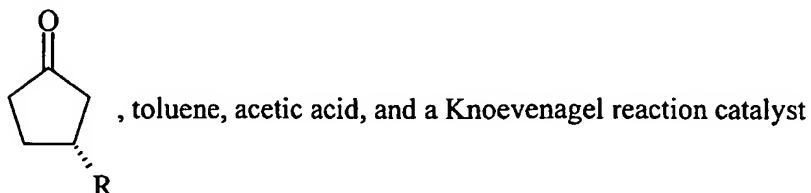
- k) converting the product of Step j) to a compound of Formula I



pharmaceutically acceptable salt by known means.

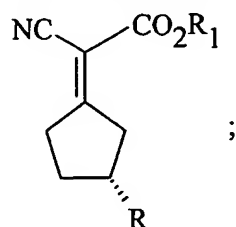
3. A process according to Claim 1 which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)

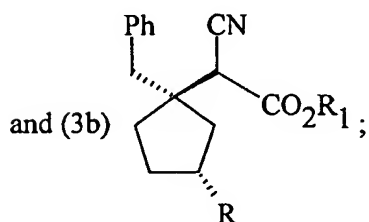
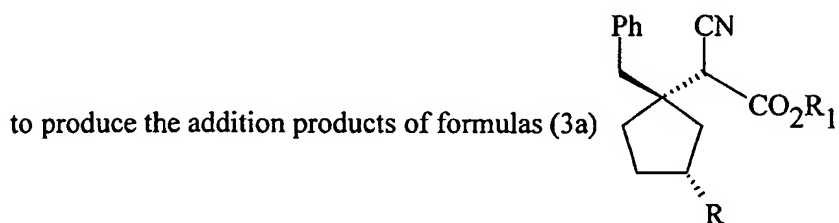


-140-

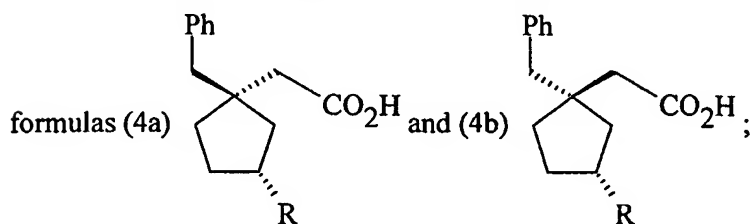
which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)



- b) adding the product of Step a) above to a mixture of
benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C

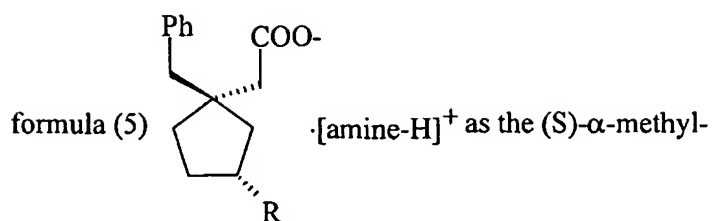


- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of



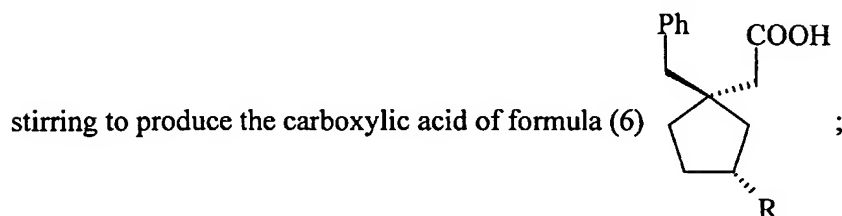
- d) contacting the products of Step c) above with (S)- α -methylbenzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of

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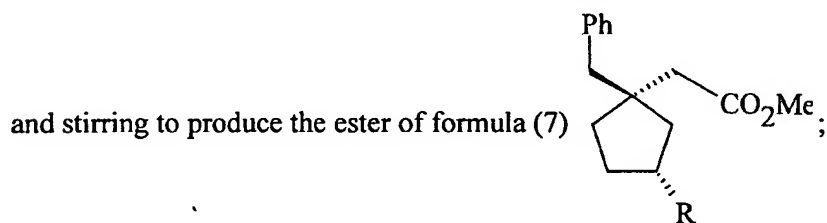


benzylamine salt;

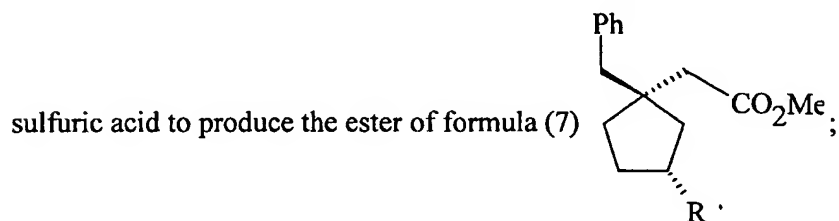
- e) adding the product of Step d) to aqueous hydrochloric acid and



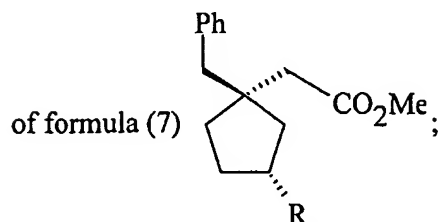
- 5 f) adding the product of Step e) to a mixture of iodomethane, dichloromethane, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),



or adding the product of Step e) to methanol and concentrated



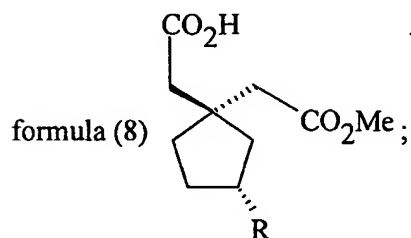
- 10 or adding the product of Step e) to a solution of diazomethane or trimethylsilyl-diazomethane in dichloromethane to produce the ester



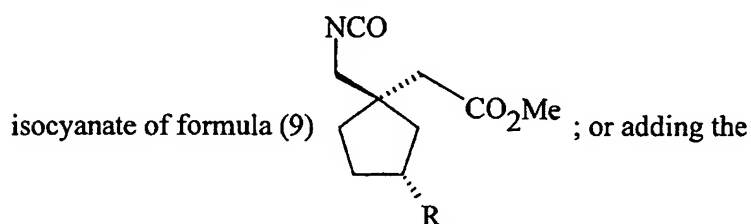
- g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and

-142-

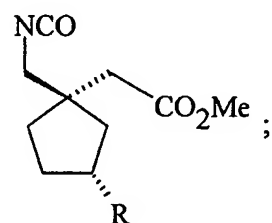
ruthenium(III) chloride, and stirring to produce the carboxylic acid of



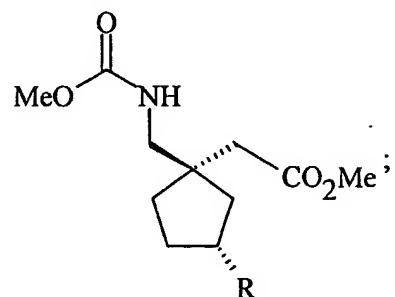
- h) adding the product of Step g) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the



product of Step g) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran, followed by adding toluene or benzene, and refluxing to produce ester of formula (9)

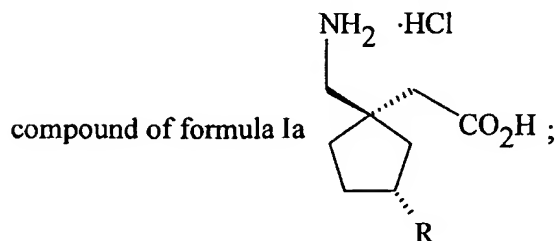


- i) adding the product of Step h) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (10)

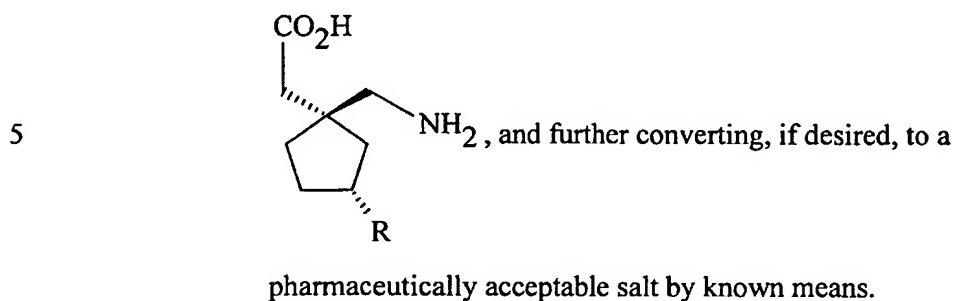


-143-

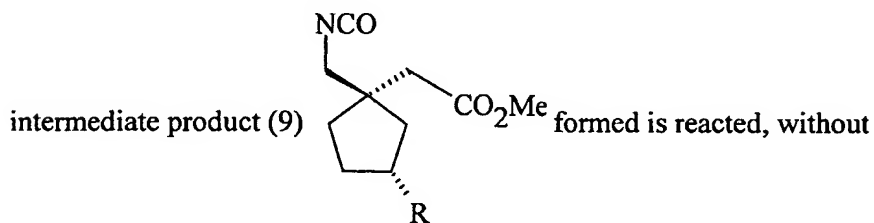
- j) adding the product of Step i) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a



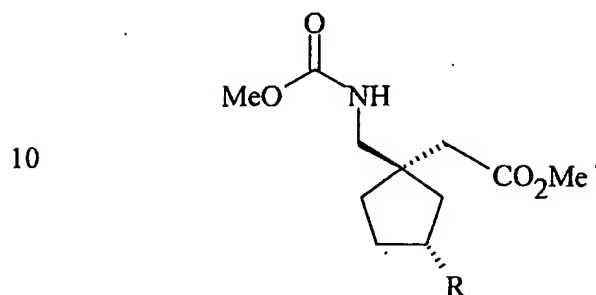
- k) converting the product of Step j) to a compound of Formula I



4. A process according to Claim 1, further characterized in that the

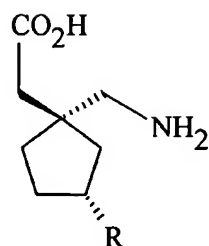


isolation, with methanol to produce the carbamate of formula (10)



5. A process for the preparation of a compound of Formula II

-144-

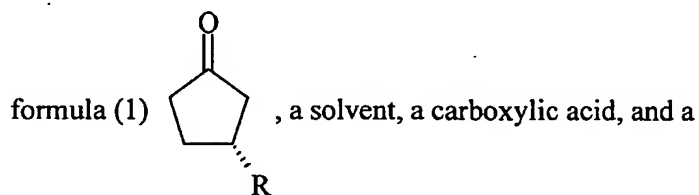


II

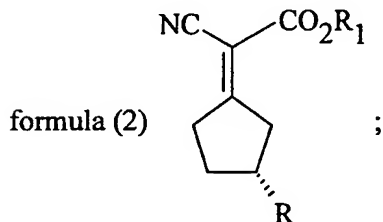
wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

5



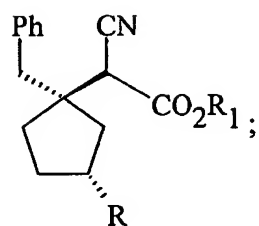
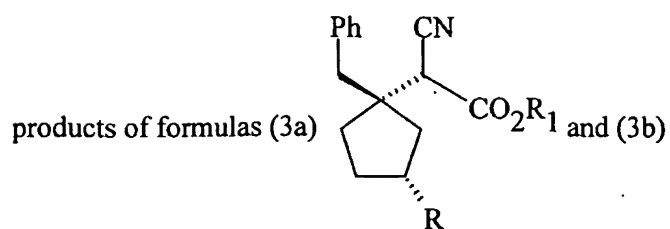
Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of



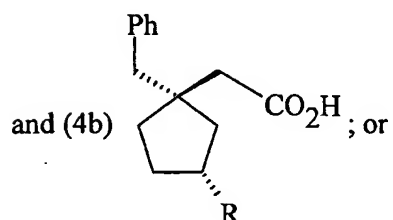
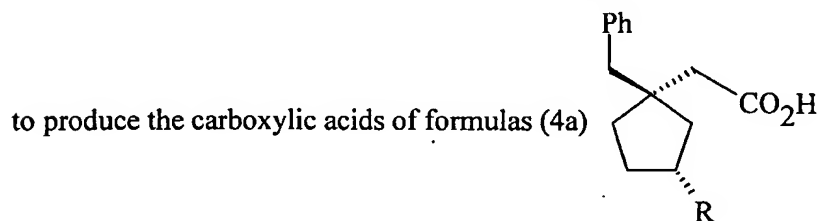
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- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

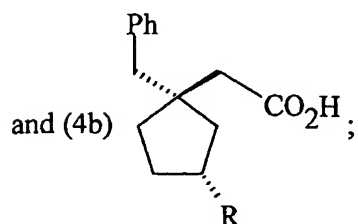
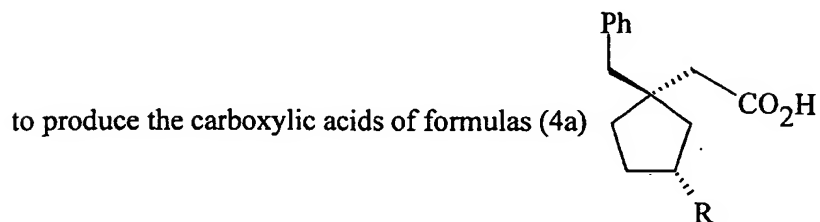
-145-



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide and a solvent, and stirring, and then acidifying

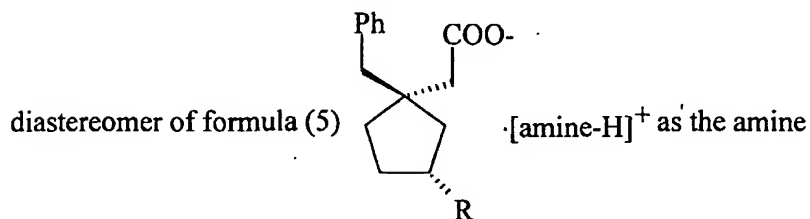


adding the products of Step b) above to an acid mixture and stirring



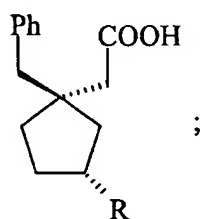
-146-

- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

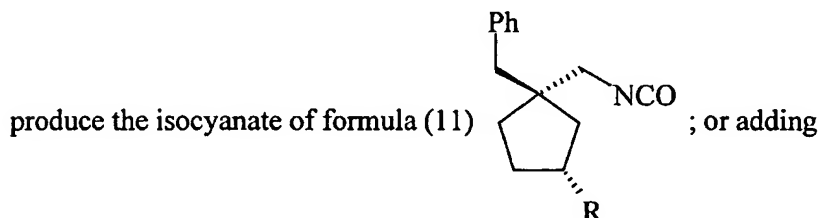


salt; and

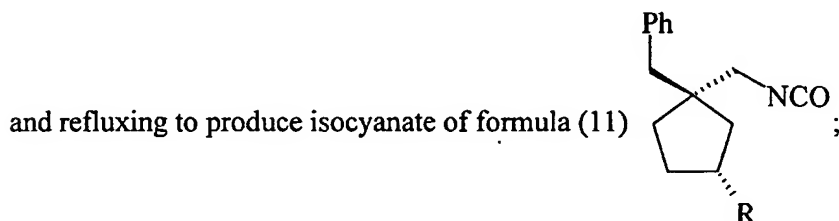
- 5 e) converting the product of Step d) to a carboxylic acid of formula (6)



- f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to

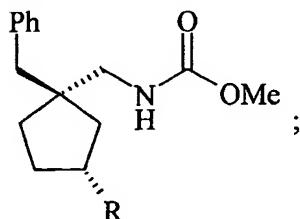


- 10 the product of Step e) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene,



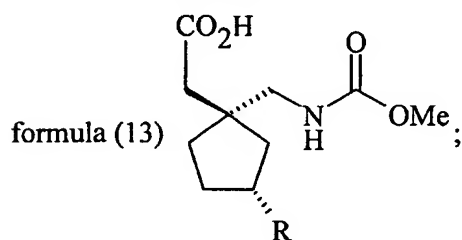
-147-

- g) adding the product of Step f) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (12)



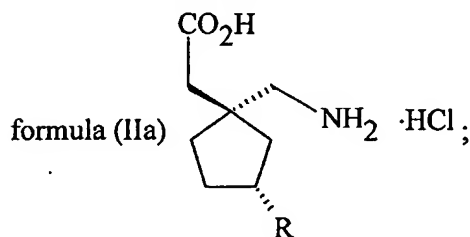
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- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

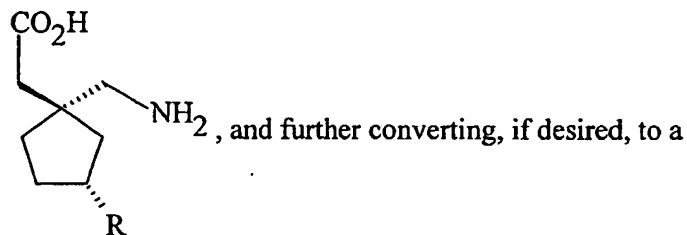


- i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of

10



- j) converting the product of Step i) to a compound of formula (II)

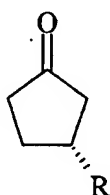


pharmaceutically acceptable salt by known means.

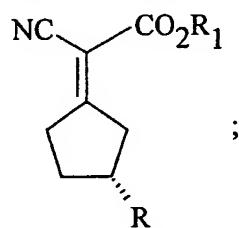
6. A process according to Claim 5 which comprises:

-148-

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral

cyclopentanone of formula (1) , a solvent selected from

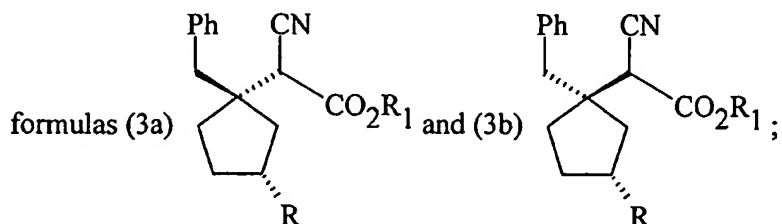
- 5 tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a
- 10 means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and
- 15 triethyl orthoformate to produce the alkene of formula (2)



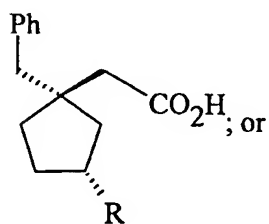
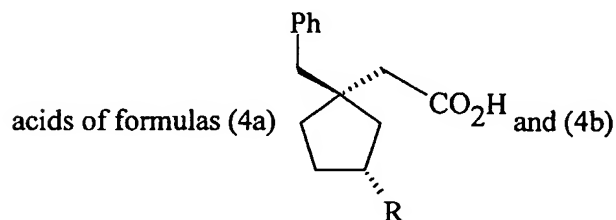
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and
- 20

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tert-butyl methyl ether to produce the addition products of

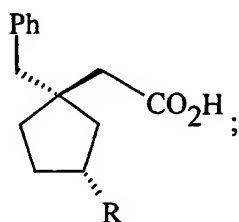
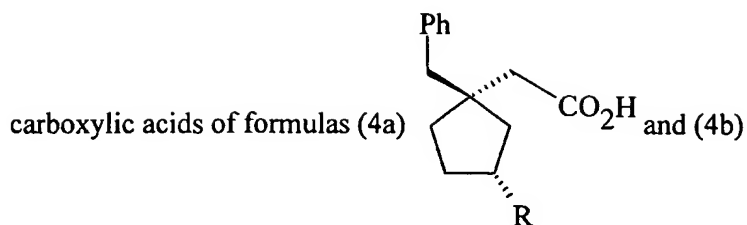


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic

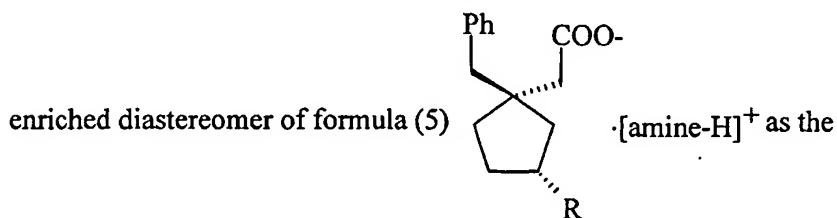


- adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the

-150-



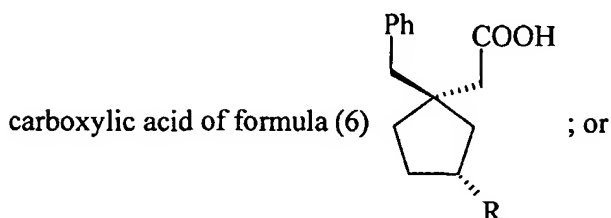
- d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the



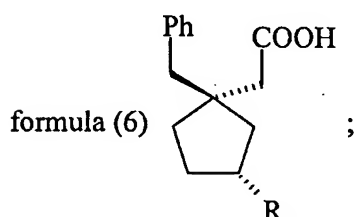
- amine salt;
- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid

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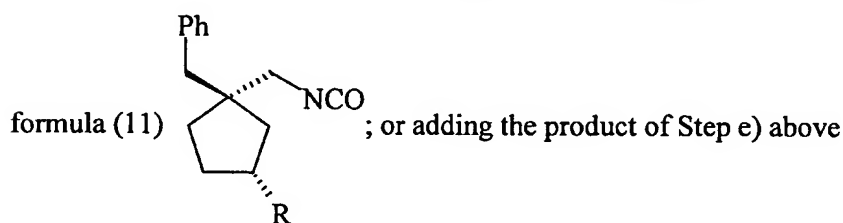
dissolved in acetic acid and water, and stirring to produce the



partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of



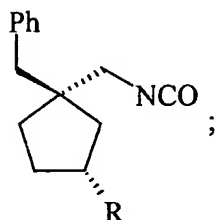
- f) adding the product of Step e) above to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, tetrahydrofuran, diethyl ether and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature of from 0°C to 150°C to produce the isocyanate of



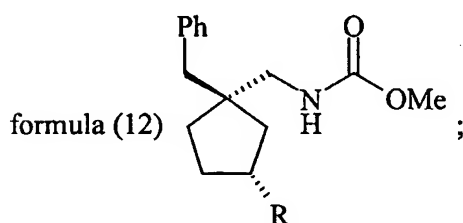
to ethyl chloroformate or isobutyl chloroformate and a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene

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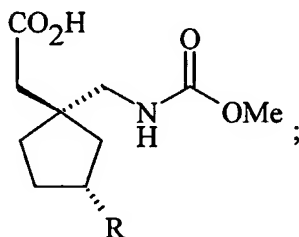
or benzene, and refluxing to produce the isocyanate of formula (11)



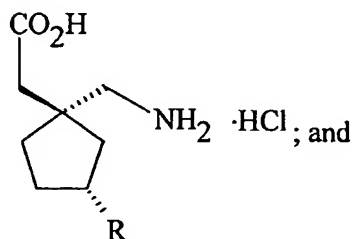
- g) adding the product of Step f) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of



- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (13)

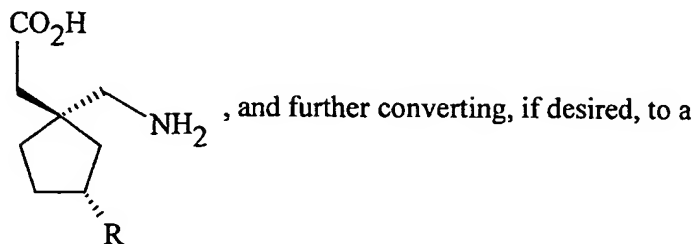


- i) adding the product of Step h) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa



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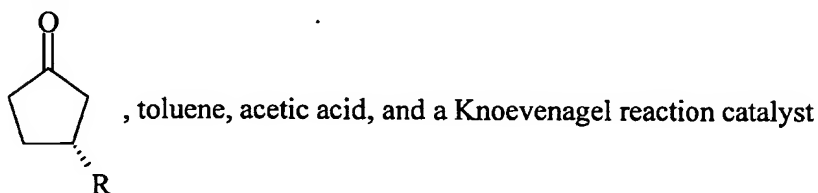
- j) converting the product of Step i) to a compound of Formula II



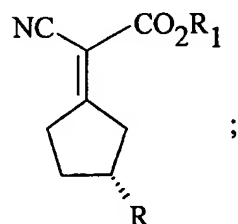
pharmaceutically acceptable salt by known means.

7. A process according to Claim 5 which comprises:

- 5 a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)

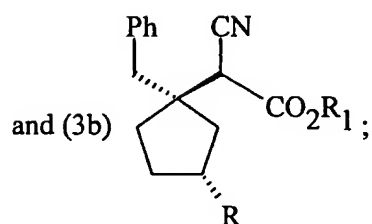
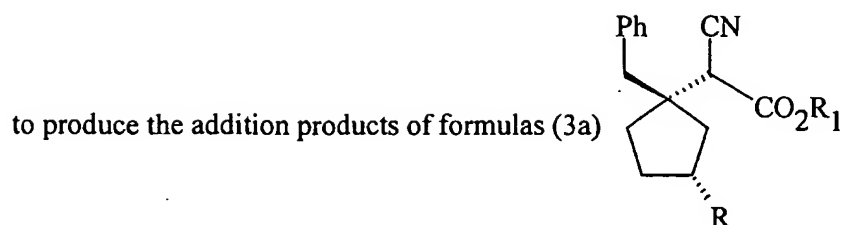


which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)

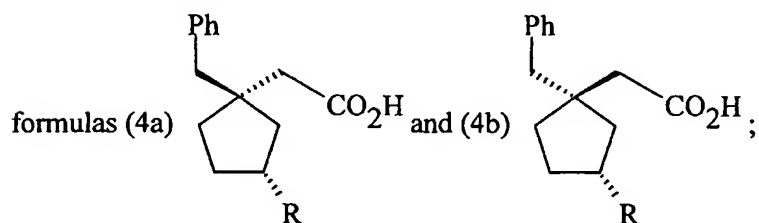


- 10 b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C

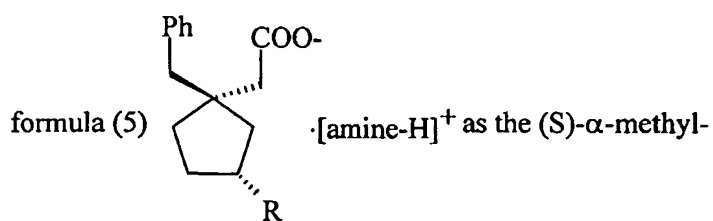
-154-



- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of

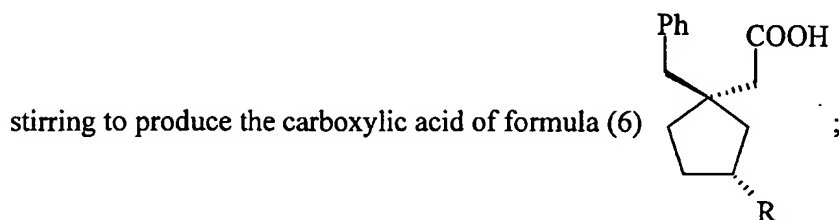


- d) contacting the products of Step c) above with (S)- α -methylbenzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of



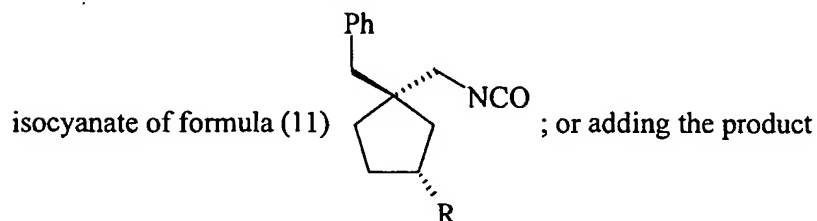
benzylamine salt;

- e) adding the product of Step d) to aqueous hydrochloric acid and

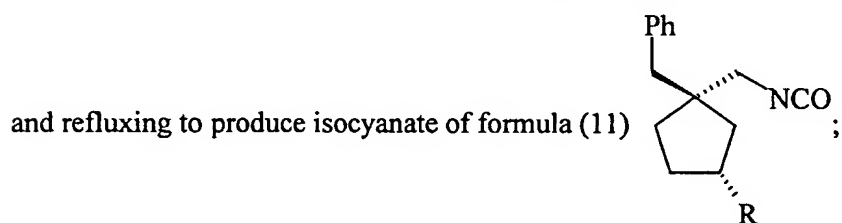


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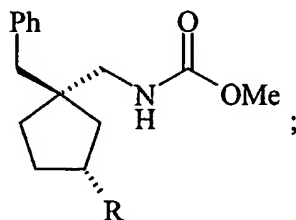
- f) adding the product of Step e) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the



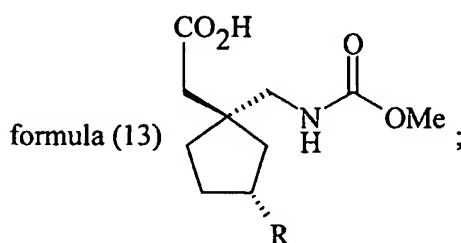
of Step e) above to ethyl chloroformate or isobutyl chloroformate and triethylamine in tetrahydrofuran at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene,



- g) adding the product of Step f) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (12)

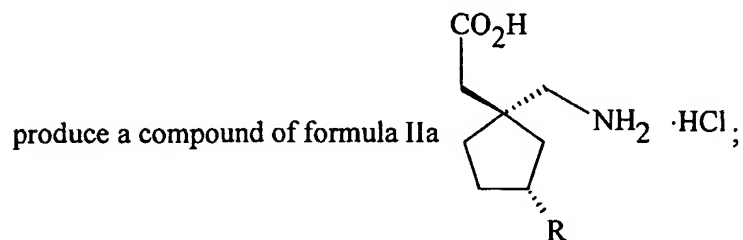


- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

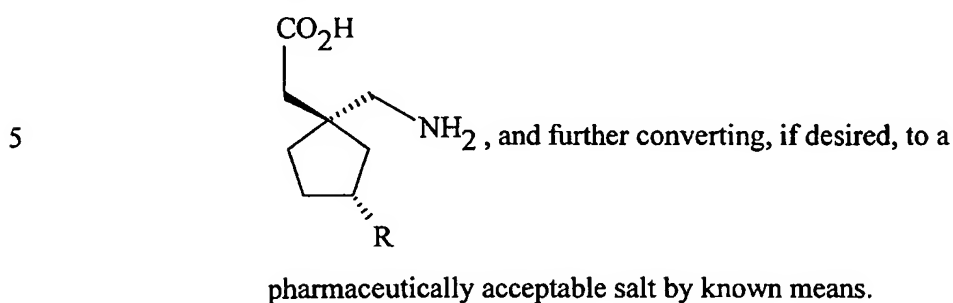


-156-

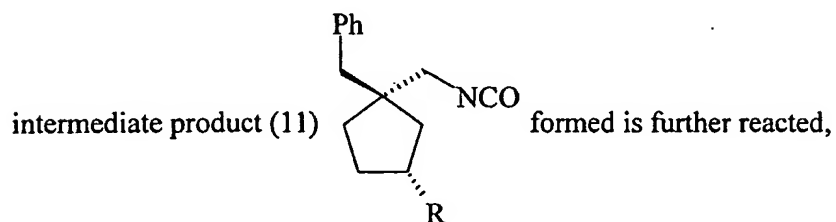
- i) adding the product of Step h) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to



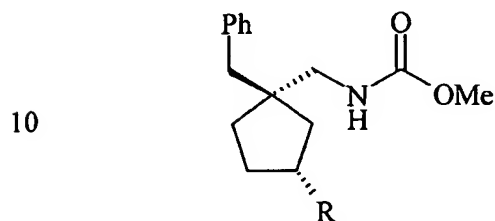
- j) converting the product of Step i) to a compound of Formula II



8. A process according to Claim 5, further characterized in that the

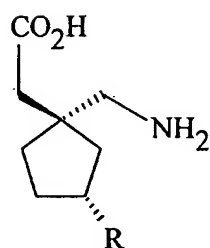


without isolation, with methanol to produce the carbamate of formula (12)



9. A process for the preparation of a compound of Formula II

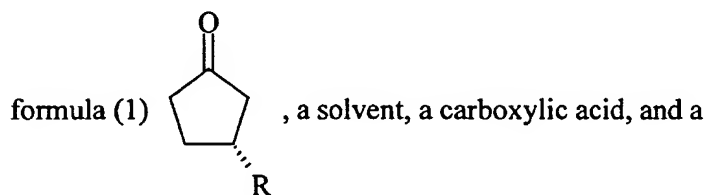
-157-



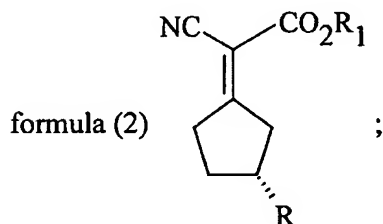
II

wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

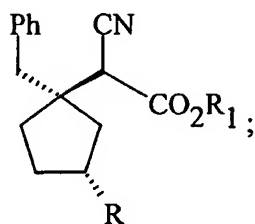
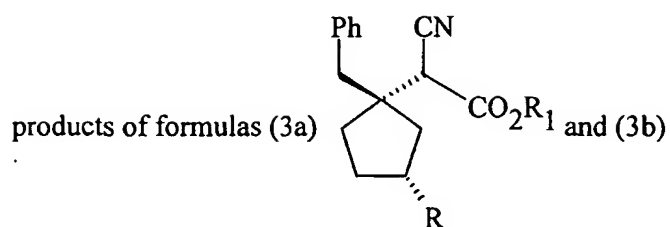


Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

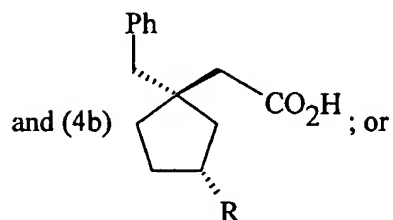
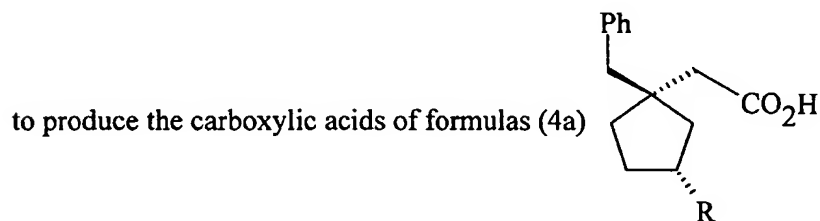


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

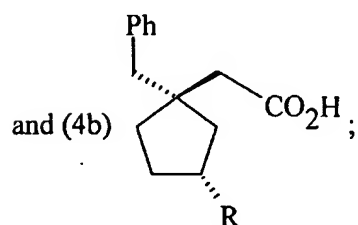
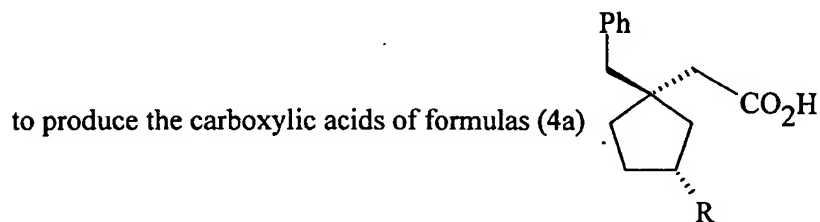
-158-



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

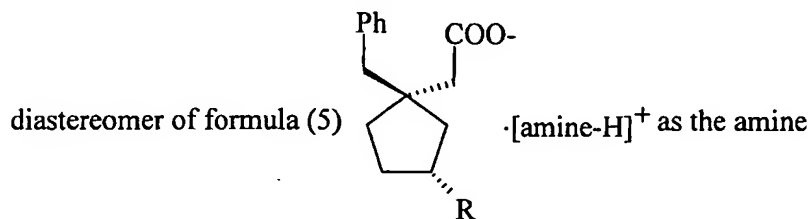


adding the products of Step b) above to an acid mixture and stirring



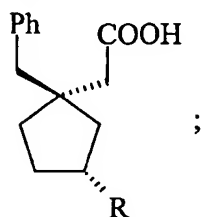
-159-

- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

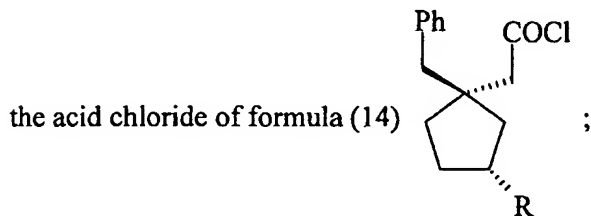


salt;

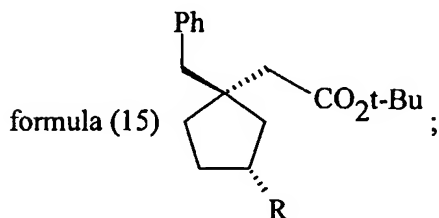
- 5 e) converting the product of Step d) to a carboxylic acid of formula (6)



- f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce



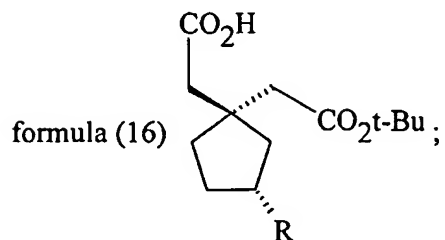
- 10 g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of



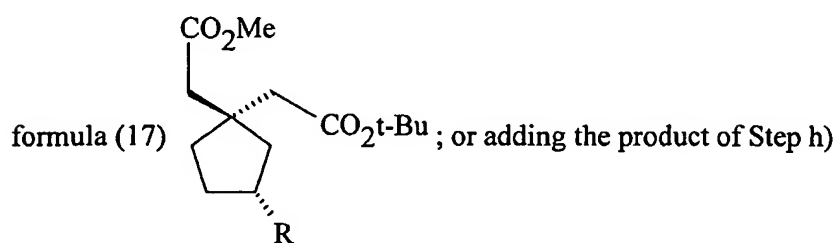
- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and

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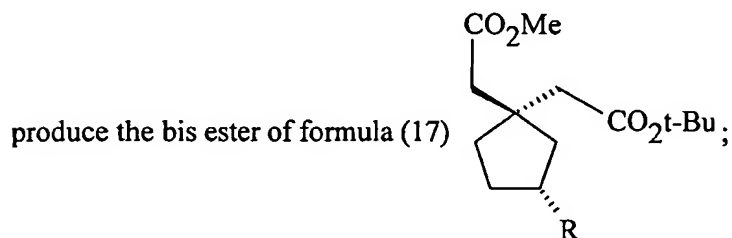
ruthenium(III) chloride, and stirring to produce the carboxylic acid of



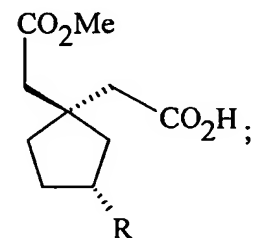
- i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of



to a mixture of iodomethane, a solvent, and a base, and stirring to

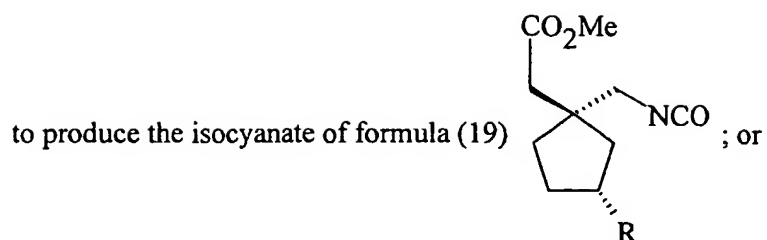


- j) adding an acid to a mixture of the product from Step i) and a solvent, and stirring to produce the carboxylic acid of formula (18)

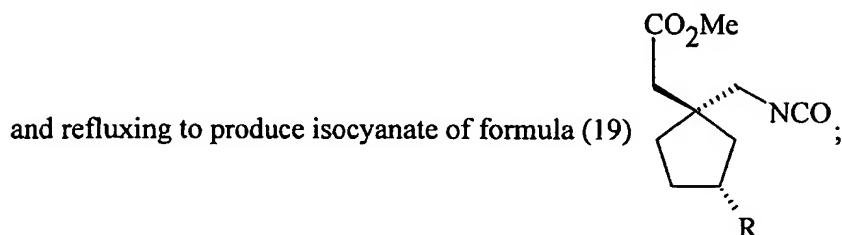


- k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring

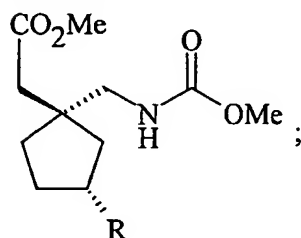
-161-



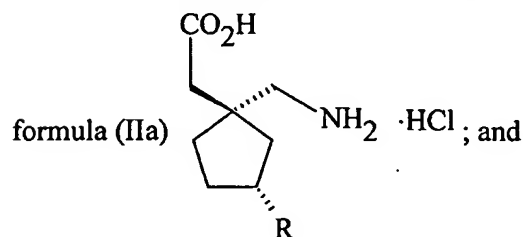
adding the product of Step j) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene,



- l) adding the product of Step k) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (20)

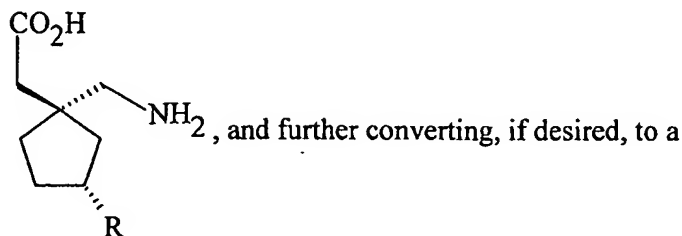


- m) adding the product of Step l) to a mixture of a solvent and aqueous hydrochloric acid is added, and stirring to produce a compound of



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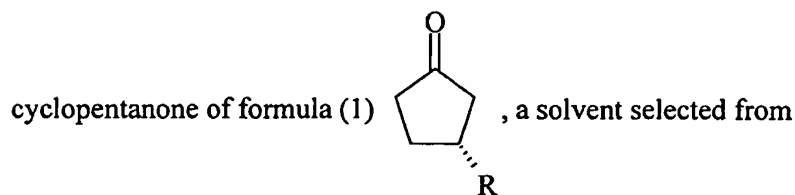
- n) converting the product of Step m) to a compound of formula (II)



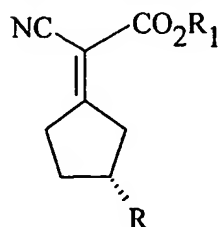
pharmaceutically acceptable salt by known means.

10. A process according to Claim 9 which comprises:

- 5 a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral

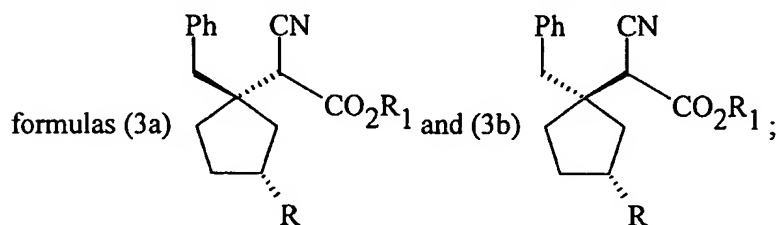


- 10 tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a
- 15 means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

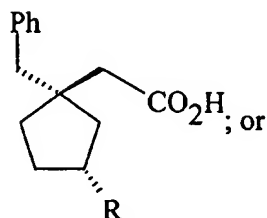
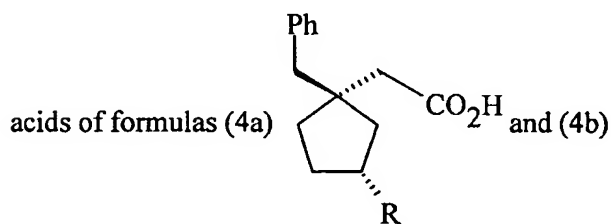


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- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of

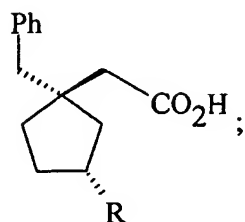
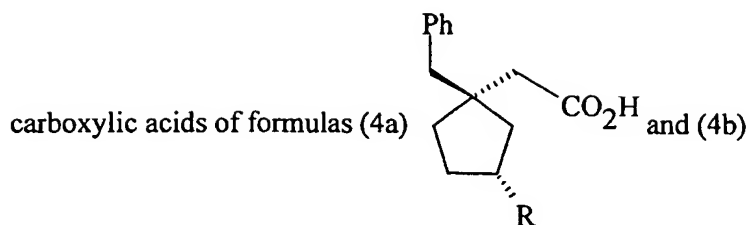


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture and then acidifying to produce the carboxylic

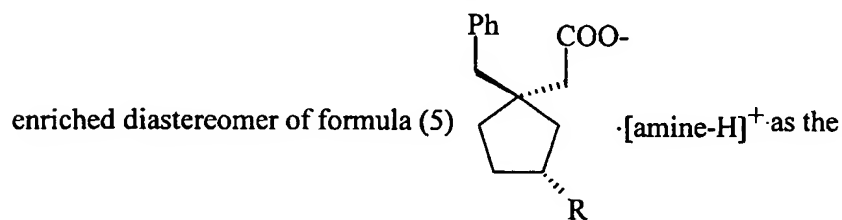


- adding the products of Step b) above to an acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring to produce the

-164-



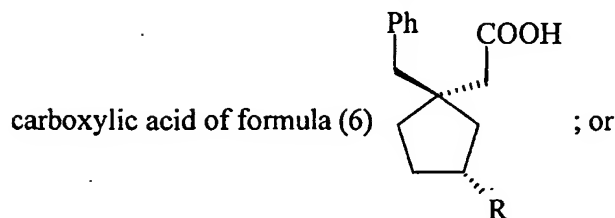
- d) contacting the products of Step c) above with an amine selected from
 (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-
 (naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine,
 diisopropylethylamine, dicyclohexylamine, benzylamine,
 dibenzylamine, morpholine, N-methylmorpholine, piperidine,
 N-methylpiperidine, and pyridine in a solvent selected from N,N-
 dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone,
 ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane,
 benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate,
 acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and
 1,4-dioxane, and recrystallizing the salt so formed to produce the



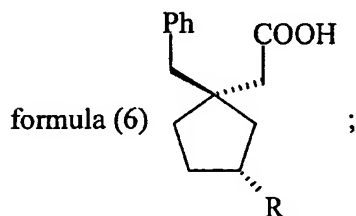
- amine salt;
 e) adding the product of Step d) to a mixture selected from aqueous
 hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid,
 hydrochloric acid dissolved in acetic acid, or hydrochloric acid

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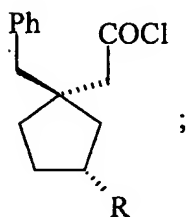
dissolved in acetic acid and water, and stirring to produce the



partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of



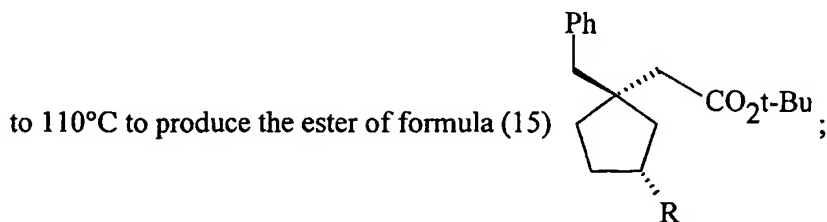
- f) adding oxalyl chloride to a mixture of the product of Step e), a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and 0.01 to 10 mole percent of *N,N*-dimethylformamide (DMF), and stirring at a temperature from -40°C to 110°C to produce the acid chloride of formula (14)



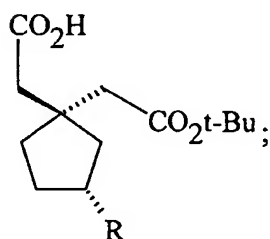
- g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent selected from dichloromethane, chloroform, ethyl ether, toluene, and *tert*-butyl methyl ether, and *N,N*-diisopropylethylamine

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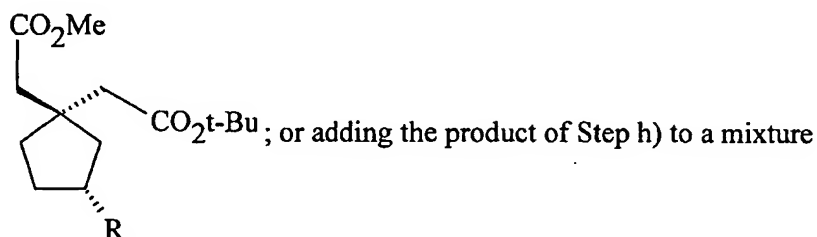
(DIPEA) or triethylamine, and stirring at a temperature from -40°C



- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring at a temperature from -40°C to 80°C to produce the carboxylic acid of formula (16)



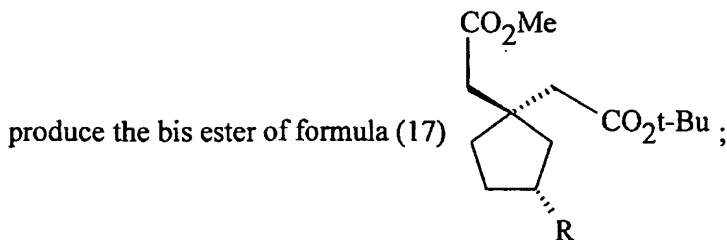
- i) adding the product of Step h) to a solvent selected from toluene, benzene, xylenes, and *n*-heptane, methanol, and (trimethylsilyl)diazomethane, and stirring at a temperature from 0°C to 150°C to produce the bis ester of formula (17)



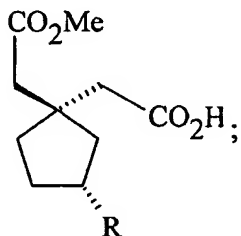
of iodomethane, a solvent selected from dichloromethane, chloroform, tetrahydrofuran, toluene and 1,4-dioxane, and a base selected from 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine, triethylamine, or 1,5-diazabicyclo[4.3.0]non-

-167-

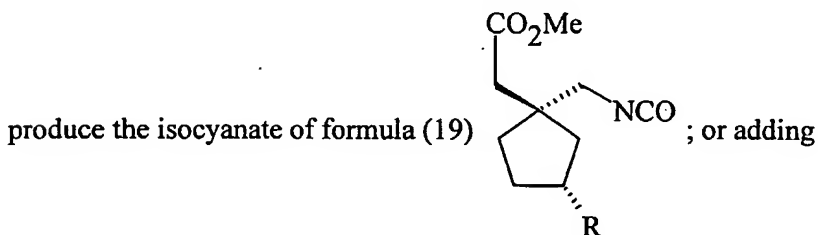
5-ene (DBN), and stirring at a temperature of from -40°C to 110°C to



- j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and a solvent selected from dichloromethane, chloroform, 1,4-dioxane, tetrahydrofuran, ethyl ether, and *tert*-butyl methyl ether, and stirring at a temperature from -40°C to 110°C to produce the carboxylic acid of formula (18)



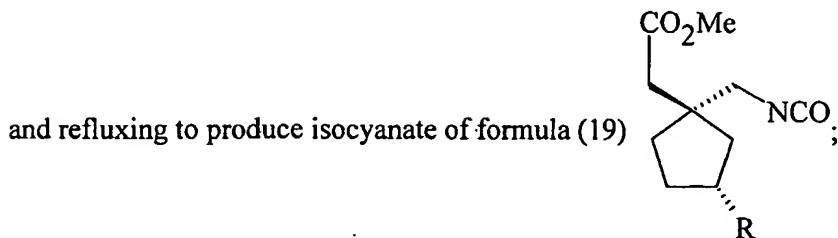
- k) adding the product of Step j) to a mixture of a base selected from triethylamine and diisopropylethylamine, a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and diphenylphosphoryl azide (DPPA), and stirring at a temperature from 0°C to 150°C to



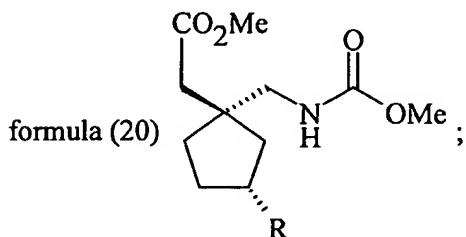
the product of Step j) above to ethyl chloroformate or isobutyl chloroformate, a base selected from triethylamine and diisopropylethylamine, and a solvent selected from tetrahydrofuran, acetone, and diethyl ether at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and

-168-

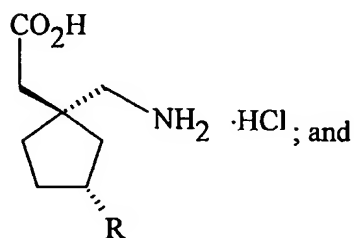
tetrahydrofuran or acetone, followed by adding toluene or benzene,



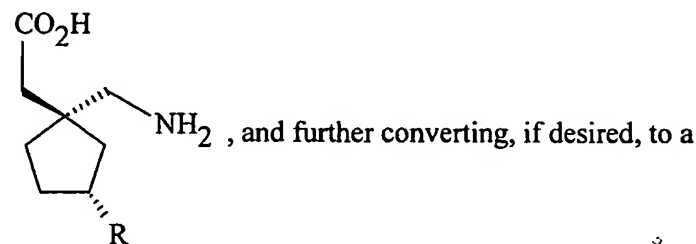
- l) adding the product of Step k) to a mixture of a solvent selected from toluene, benzene, xylenes, and *n*-heptane, and methanol, and stirring at a temperature from 0°C to 150°C to produce the carbamate of



- m) adding the product of Step l) to a mixture of a solvent selected from water, acetic acid, and 1,4-dioxane, and aqueous hydrochloric acid at a concentration of from 0.01 M to 12 M, and stirring at a temperature from 0°C to 115°C to produce a compound of formula IIa



- n) converting the product of Step m) to a compound of Formula II

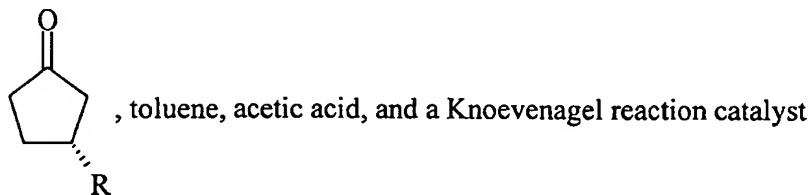


pharmaceutically acceptable salt by known means.

11. A process according to Claim 9 which comprises:

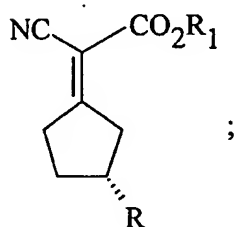
-169-

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)

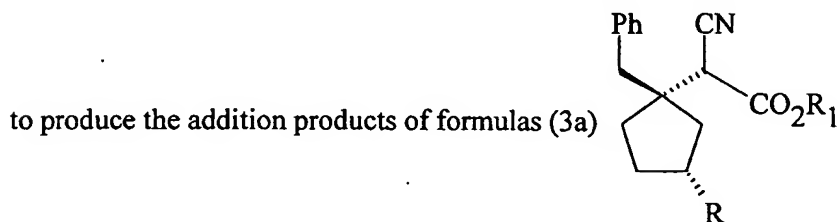


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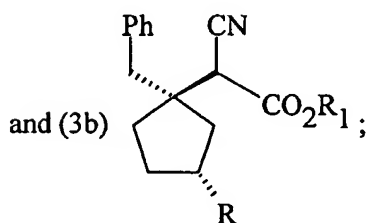
which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)



- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C



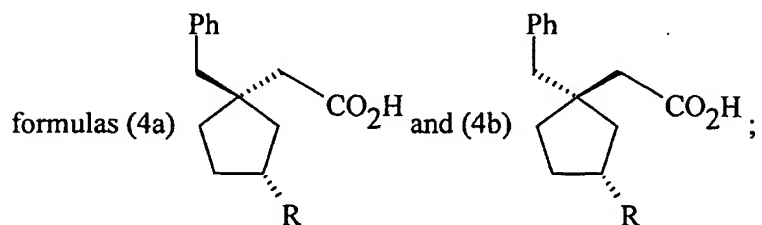
10



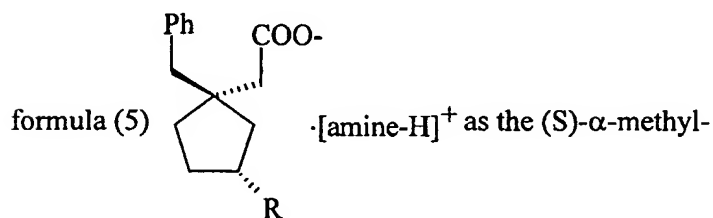
- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol and heating the mixture at 100°C to

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200°C, and then acidifying to produce the hydrolysis products of

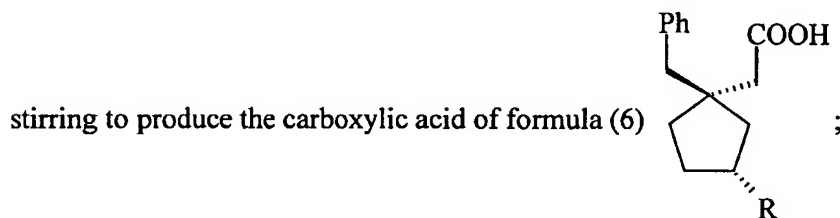


- d) contacting the products of Step c) above with (S)- α -methyl-benzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of

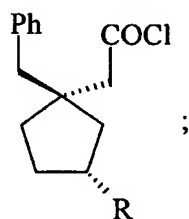


benzylamine salt;

- e) adding the product of Step d) to aqueous hydrochloric acid and

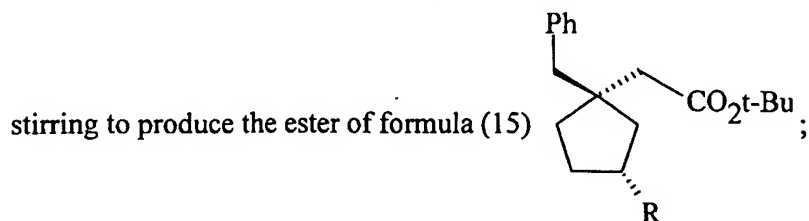


- f) adding oxalyl chloride to a mixture of the product of Step e), dichloromethane, and a catalytic amount of N,N-dimethylformamide (DMF), and stirring to produce the acid chloride of formula (14)

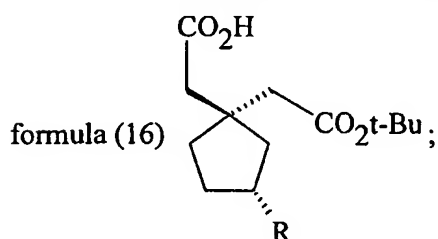


-171-

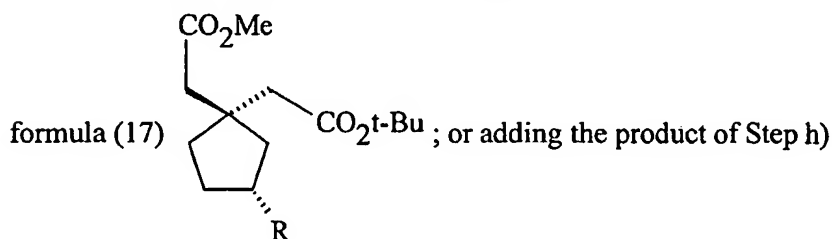
- g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, dichloromethane, and *N,N*-diisopropylethylamine (DIPEA), and



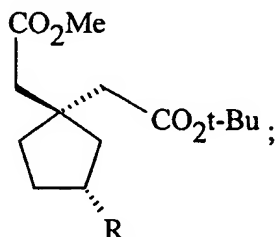
- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of



- i) adding the product of Step h) to a mixture of methanol, toluene, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of

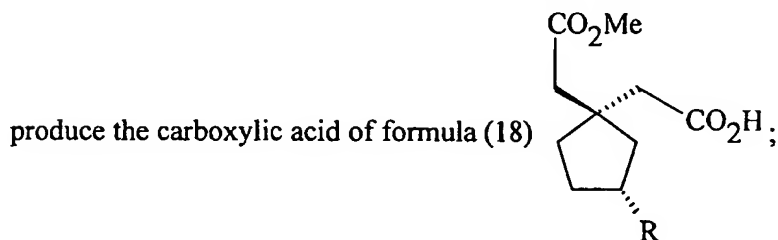


to a mixture of iodomethane, dichloromethane, triethylamine, and stirring to produce the bis ester of formula (17)

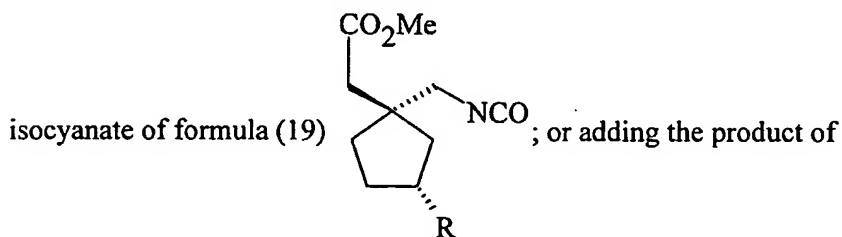


-172-

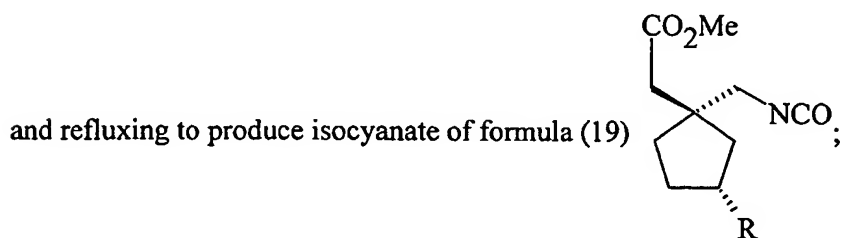
- j) adding hydrochloric acid or trifluoroacetic acid (TFA) to a mixture of the product from Step i) and dichloromethane, and stirring to



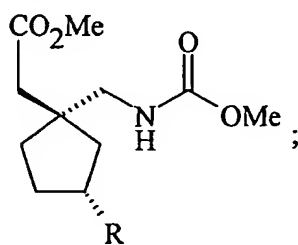
- k) adding the product of Step j) to a mixture of triethylamine, toluene, and diphenylphosphoryl azide (DPPA), and refluxing to produce the



Step j) above to ethyl chloroformate or isobutyl chloroformate, triethylamine, and tetrahydrofuran at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene,

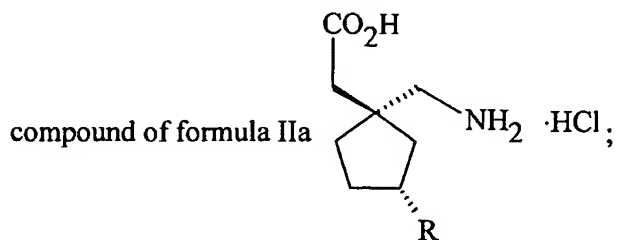


- l) adding the product of Step k) to a mixture of methanol and toluene, and refluxing to produce the carbamate of formula (20)

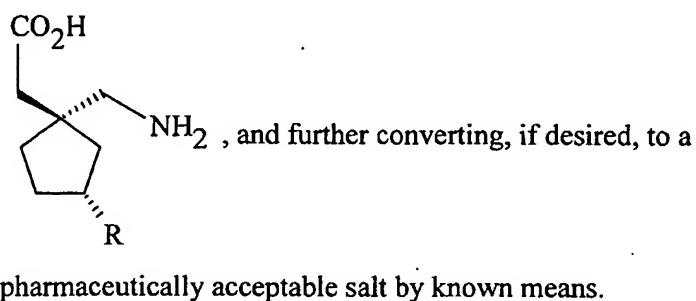


-173-

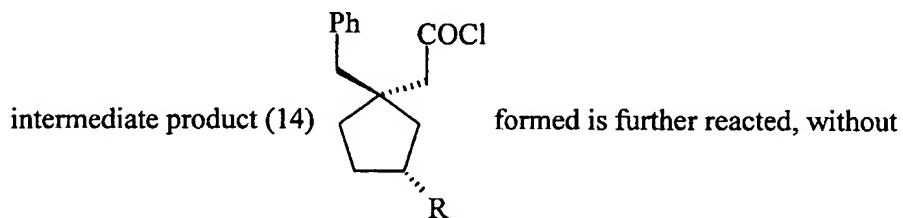
- m) adding the product of Step l) to a mixture of 1,4-dioxane and aqueous hydrochloric acid at a concentration of 6 M, and stirring to produce a



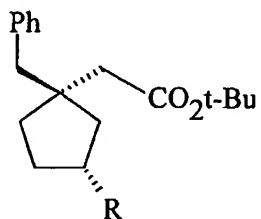
- n) converting the product of Step m) to a compound of Formula II



12. A process according to Claim 9, further characterized in that the

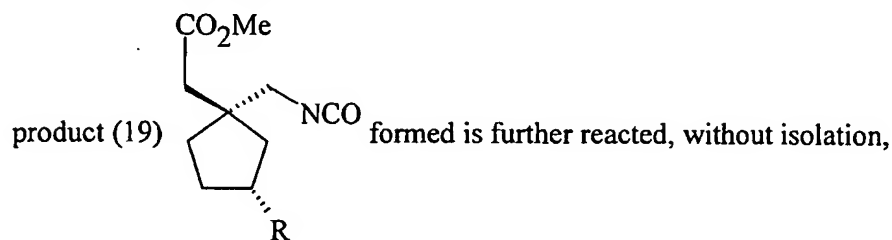


isolation, with *tert*-butyl alcohol to produce the ester of formula (15)

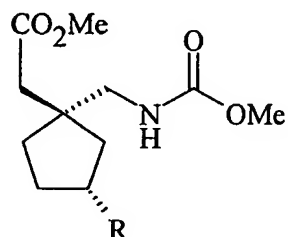


-174-

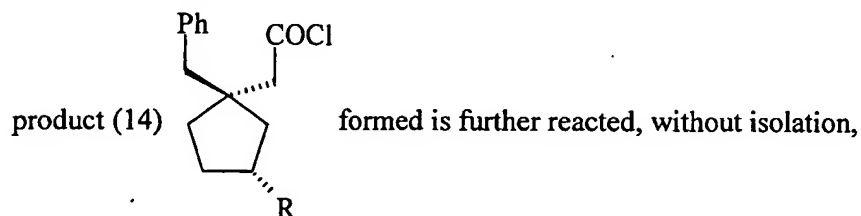
13. A process according to Claim 9, characterized in that the intermediate



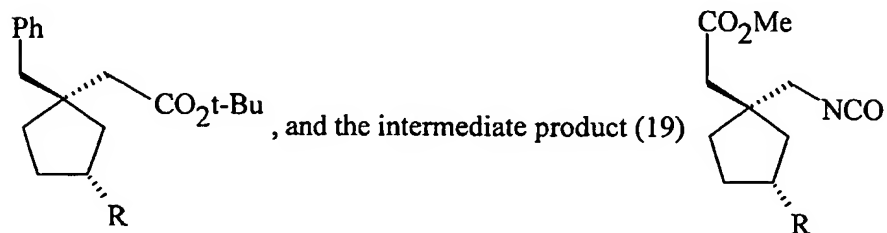
with methanol to produce the carbamate of formula (20)



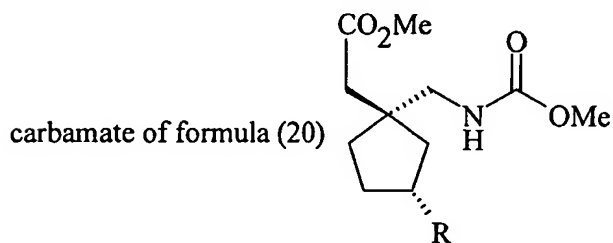
- 5 14. A process according to Claim 9, characterized in that the intermediate



with *tert*-butyl alcohol to produce the ester of formula (15)

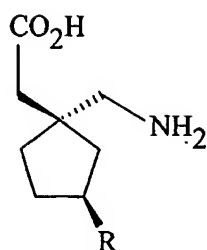


formed is further reacted, without isolation, with methanol to produce the



- 10 15. A process for the preparation of a compound of Formula III

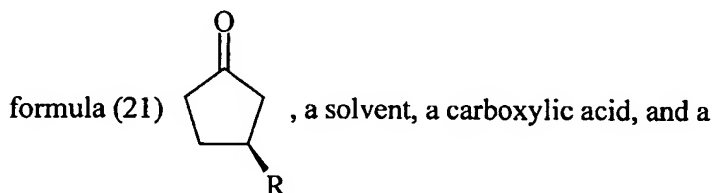
-175-



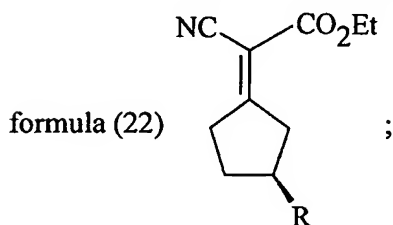
III

wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

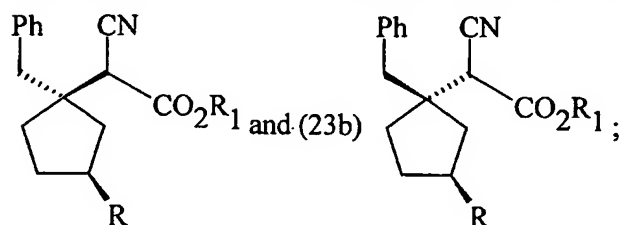
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of



Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

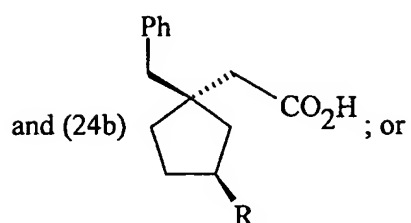
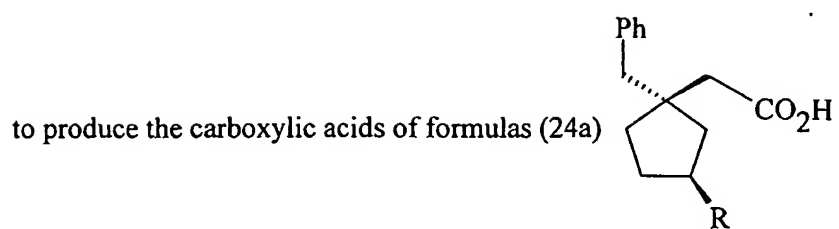


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a)

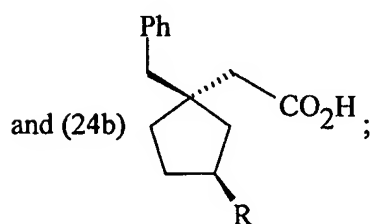
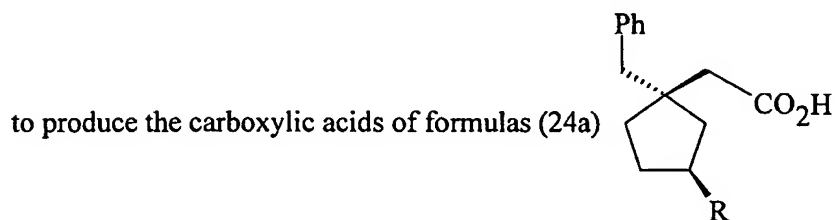


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

-176-

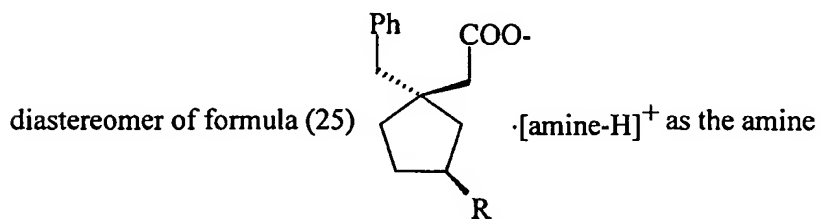


adding the products of Step b) above to an acid mixture, and stirring



5

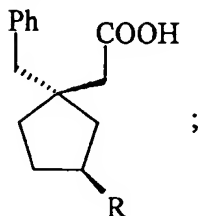
- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched



salt; and

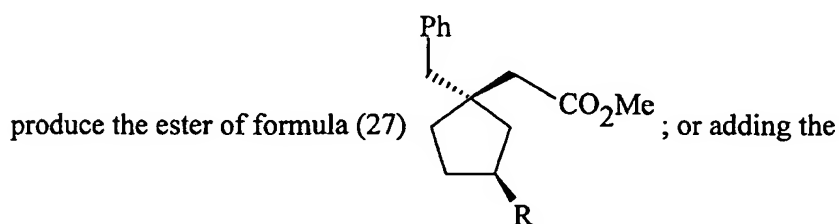
-177-

- e) converting the product of Step d) to a carboxylic acid of formula (26)

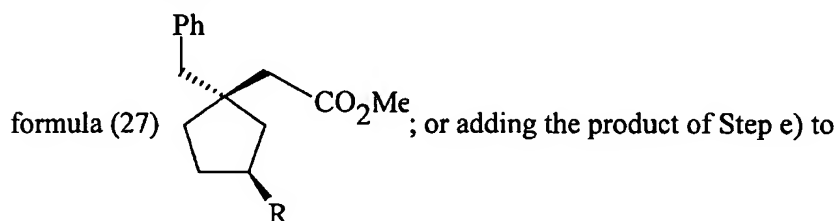


- f) adding the product of Step e) to a mixture of iodomethane, a solvent, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and stirring to

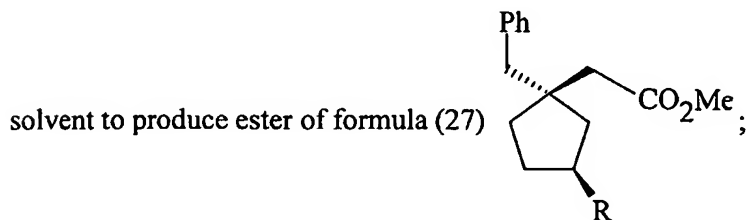
5



product of Step e) to methanol and an acid to produce the ester of

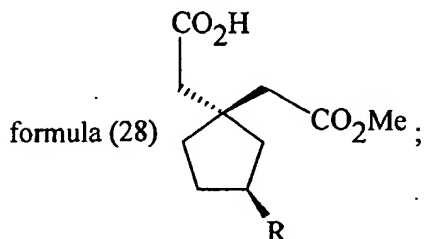


a solution of diazomethane or trimethylsilyl-diazomethane in a



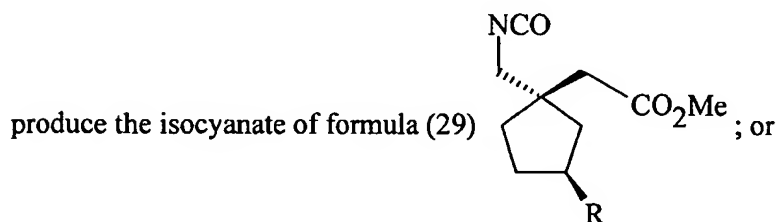
10

- g) adding the product of Step f) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of



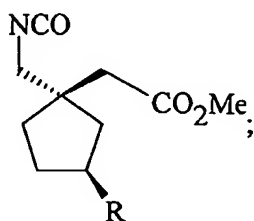
-178-

- h) adding the product of Step g) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to



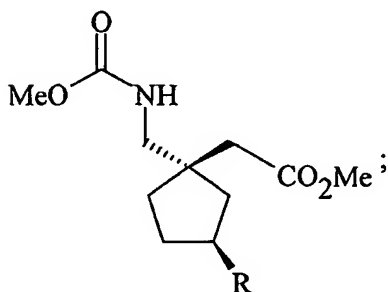
5

adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce isocyanate of formula (29)

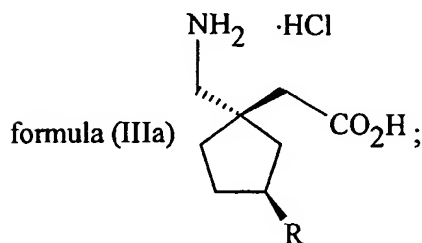


10

- i) adding the product of Step h) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (30)



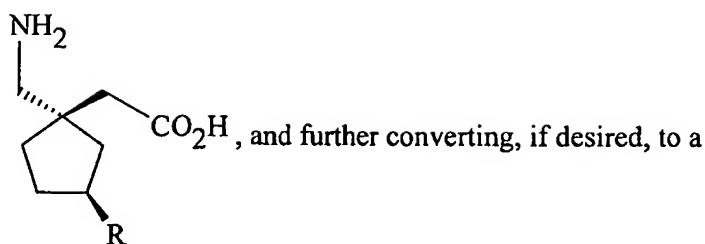
- j) adding the product of Step i) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of



15

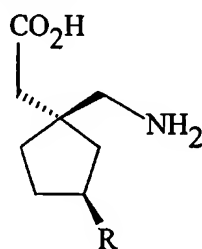
- k) converting the product of Step j) to a compound of formula (III)

-179-



pharmaceutically acceptable salt by known means.

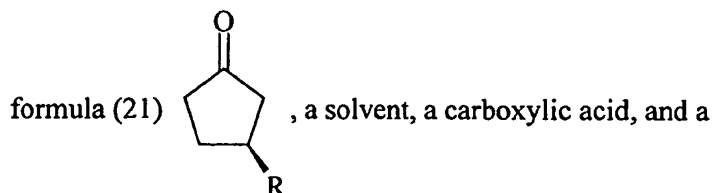
16. A process for the preparation of a compound of Formula IV



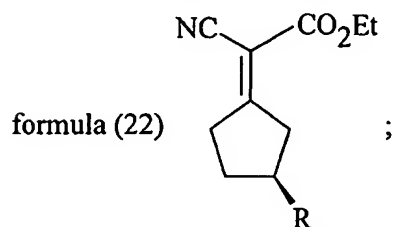
IV

- 5 wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of



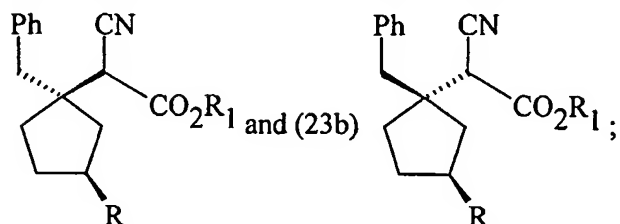
- 10 Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of



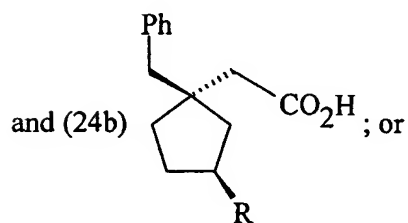
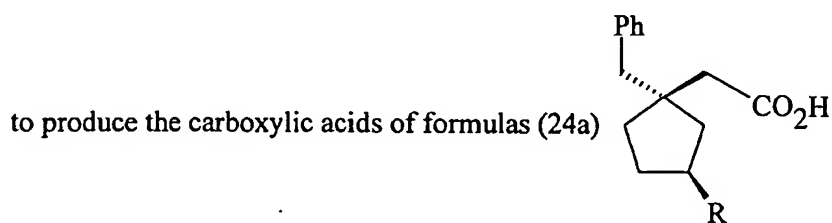
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent

-180-

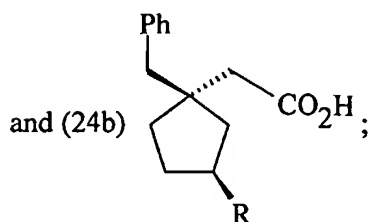
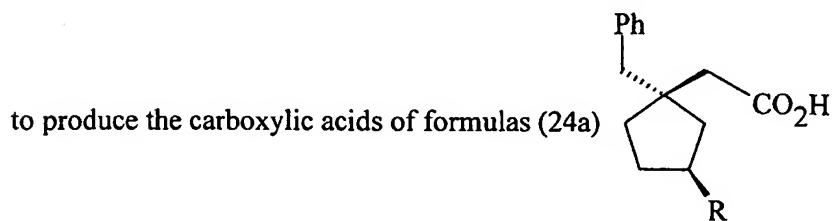
to produce the addition of products of formulas (23a)



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

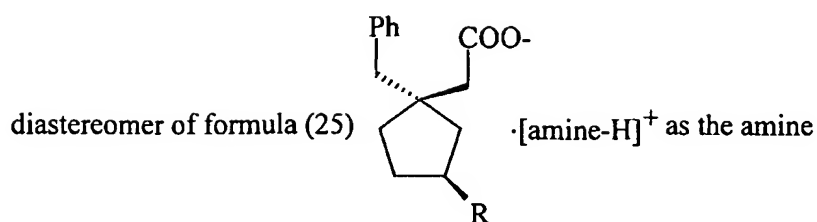


adding the products of Step b) above to an acid mixture, and stirring



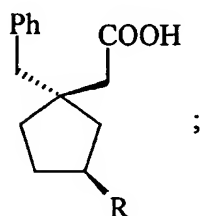
- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

-181-

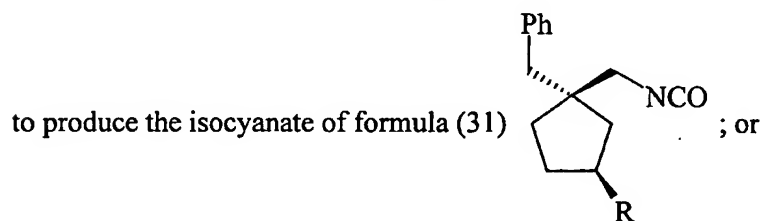


salt; and

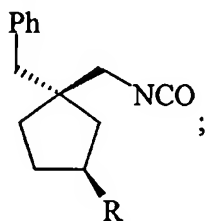
- e) converting the product of Step d) to a carboxylic acid of formula (26)



- 5 f) adding the product of Step e) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA) is added, and stirring

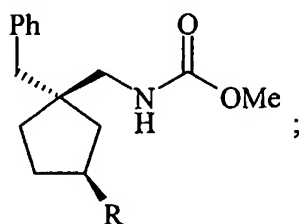


adding the product of Step g) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C , followed by adding a solution of sodium azide in water and tetrahydrofuran or acetone, followed by adding toluene or benzene, and refluxing to produce the isocyanate of formula (31)

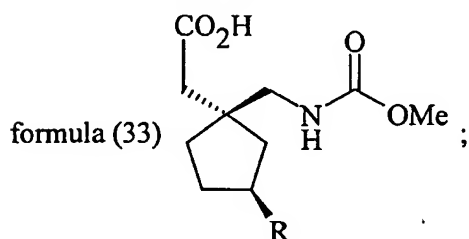


-182-

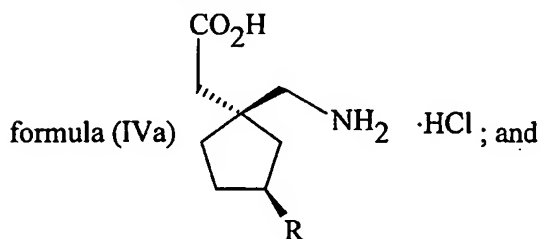
- g) adding the product of Step f) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (32)



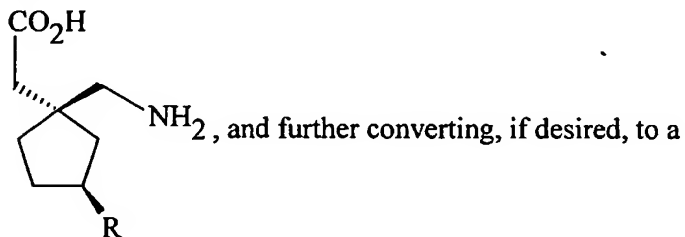
- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of



- i) adding the product of Step h) to a mixture of a solvent and aqueous hydrochloric acid, and stirring to produce a compound of



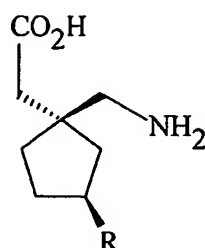
- j) converting the product of Step i) to a compound of formula (IV)



pharmaceutically acceptable salt by known means.

17. A process for the preparation of a compound of Formula IV

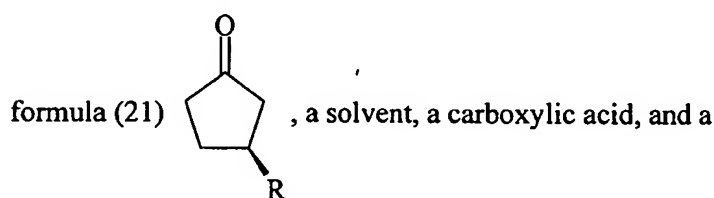
-183-



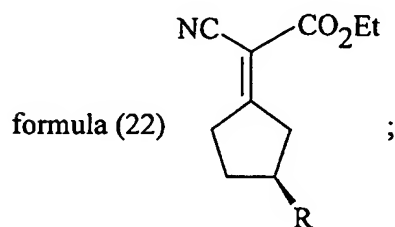
IV

wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

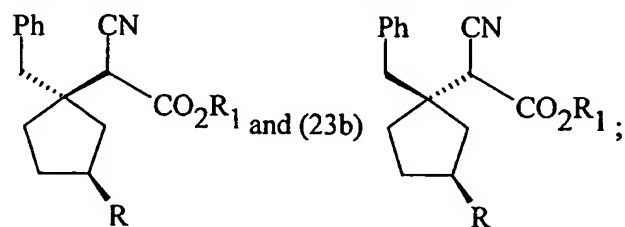
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of



Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

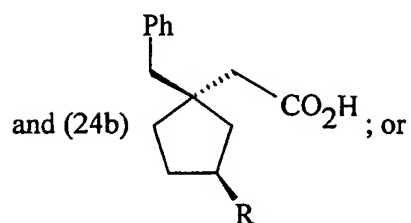
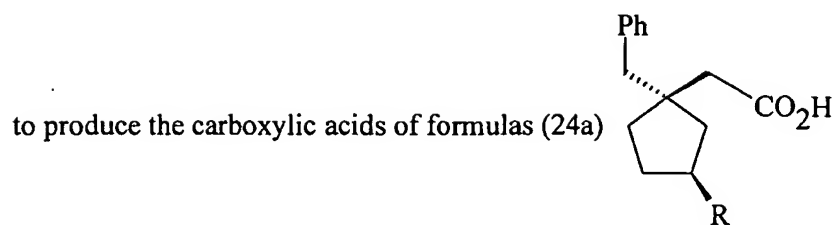


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a)

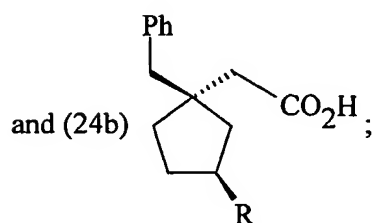
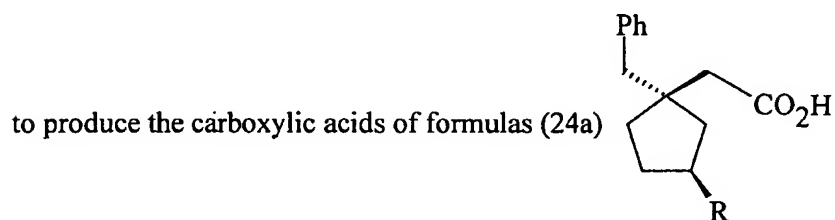


- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, in a solvent, and stirring, and then acidifying

-184-

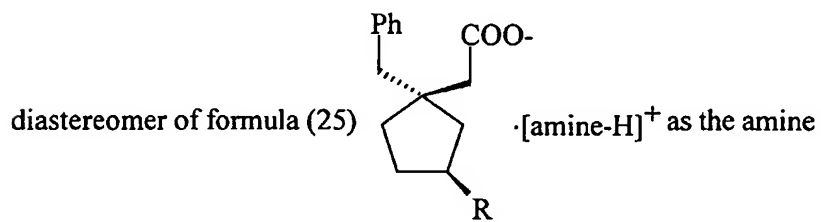


adding the products of Step b) above to an acid mixture, and stirring



5

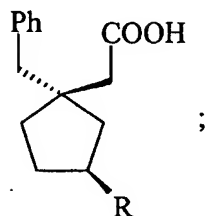
- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched



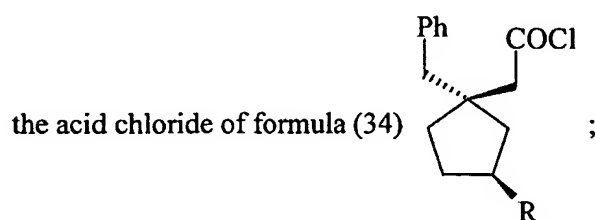
salt; and

-185-

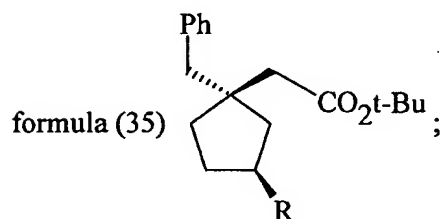
- e) converting the product of Step d) to a carboxylic acid of formula (26)



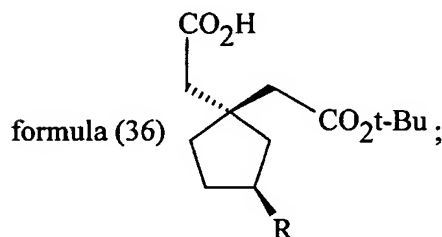
- f) adding oxalyl chloride to a mixture of the product of Step e), a solvent, and N,N-dimethylformamide (DMF), and stirring to produce



- g) adding the product of Step f) to a mixture of *tert*-butyl alcohol, a solvent, and a tertiary amine base, and stirring to produce the ester of

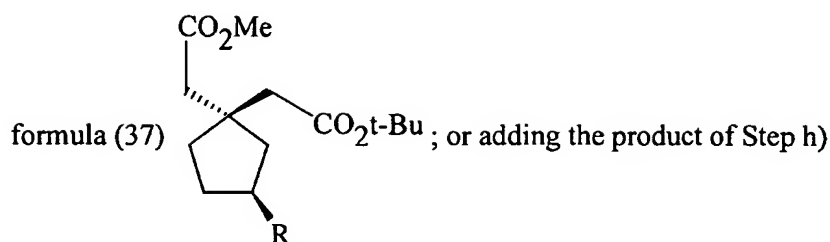


- h) adding the product of Step g) to a mixture of carbon tetrachloride or ethyl acetate, and acetonitrile, water, sodium periodate, and ruthenium(III) chloride, and stirring to produce the carboxylic acid of

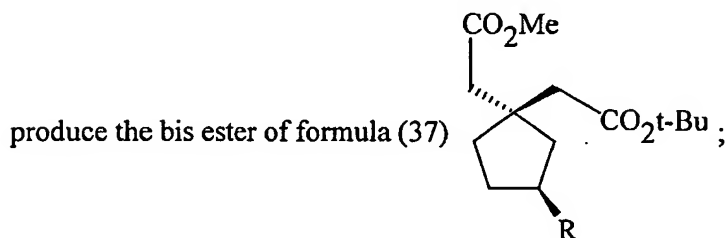


- i) adding the product of Step h) to a mixture of a solvent, methanol, and (trimethylsilyl)diazomethane, and stirring to produce the bis ester of

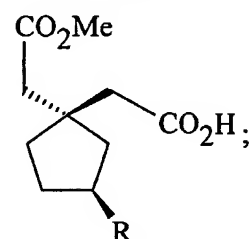
-186-



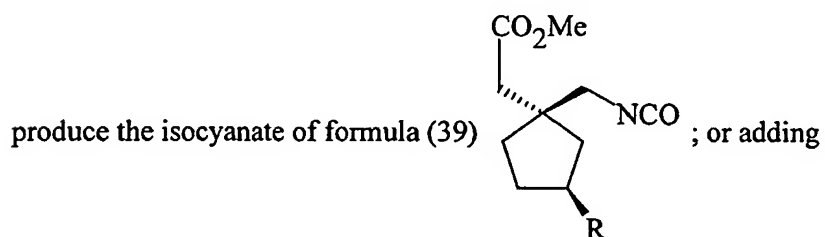
to a mixture of iodomethane, a solvent, and a base, and stirring to



- j) adding an acid to a mixture of the product from Step i) and a solvent and stirring to produce the carboxylic acid of formula (38)



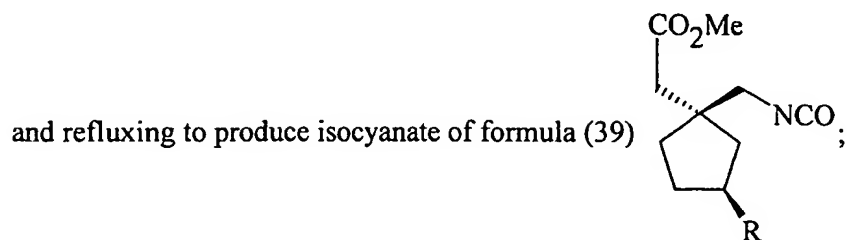
- k) adding the product of Step j) to a mixture of a tertiary amine base, a solvent, and diphenylphosphoryl azide (DPPA), and stirring to



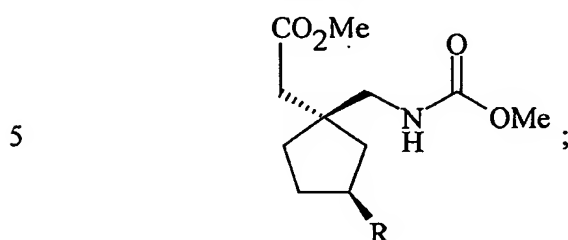
the product of Step j) above to ethyl chloroformate or isobutyl chloroformate and a base in a solvent at a temperature of from -40°C to 78°C, followed by adding a solution of sodium azide in water and

-187-

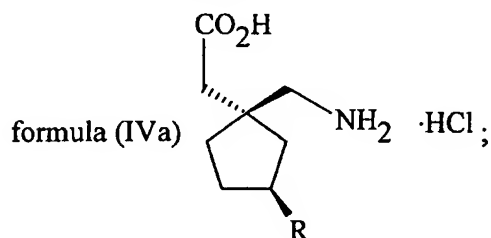
tetrahydrofuran or acetone, followed by adding toluene or benzene,



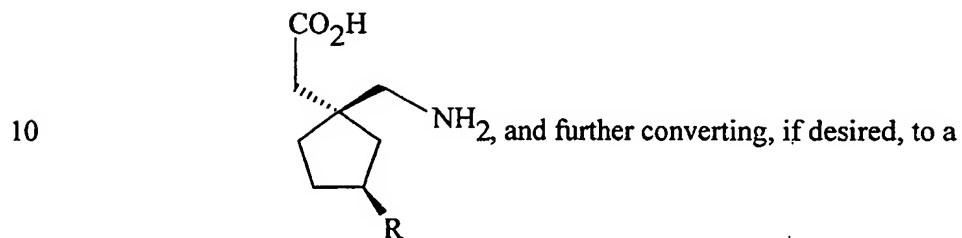
- l) adding the product of Step k) to a mixture of a solvent and methanol, and stirring to produce the carbamate of formula (40)



- m) adding the product of Step l) to a mixture of a solvent and hydrochloric acid, and stirring to produce a compound of



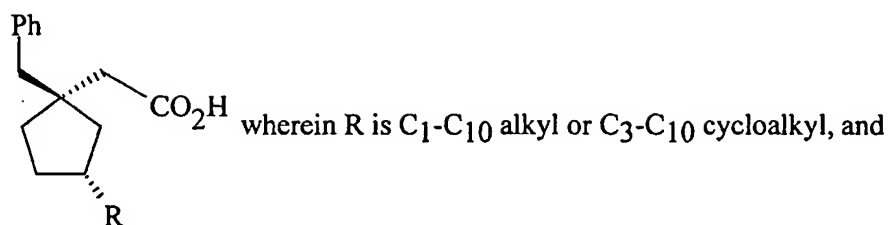
- n) converting the product of Step m) to a compound of Formula IV



pharmaceutically acceptable salt by known means.

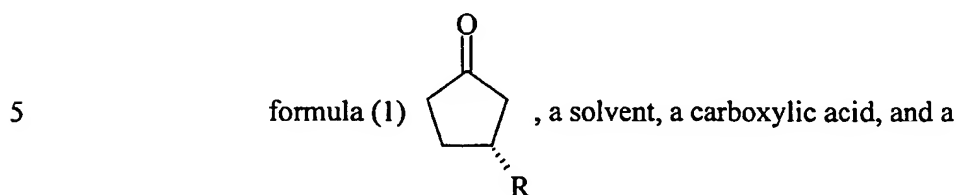
18. A process for the preparation of a compound of formula (6)

-188-

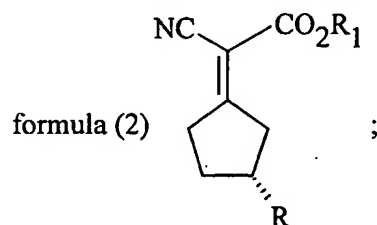


pharmaceutically acceptable salts thereof, which comprises:

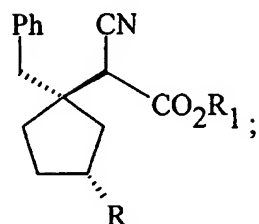
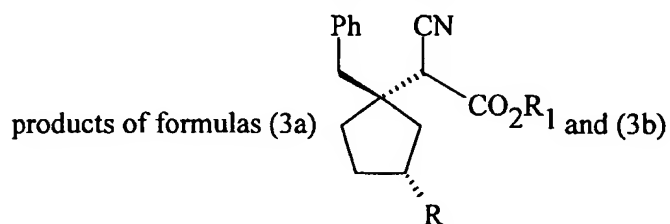
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of



Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of

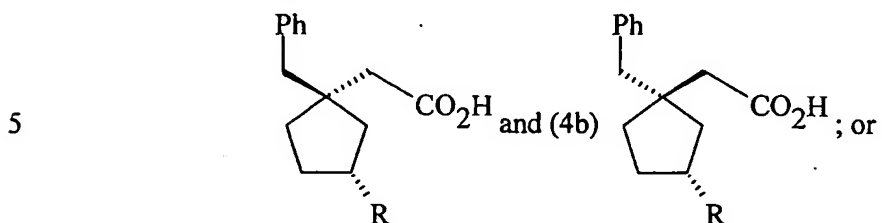


- 10 b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide, in a solvent to produce the addition

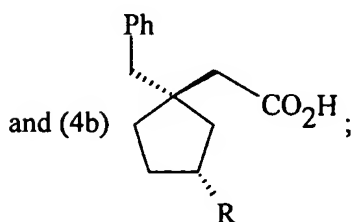
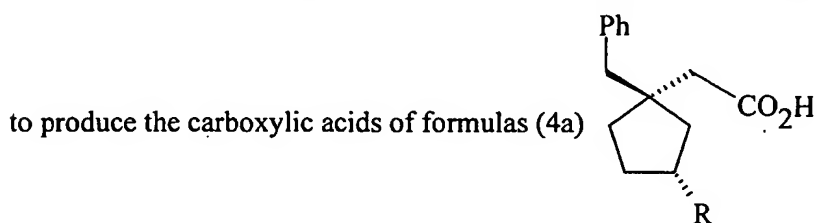


-189-

- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the carboxylic acids of formulas (4a)

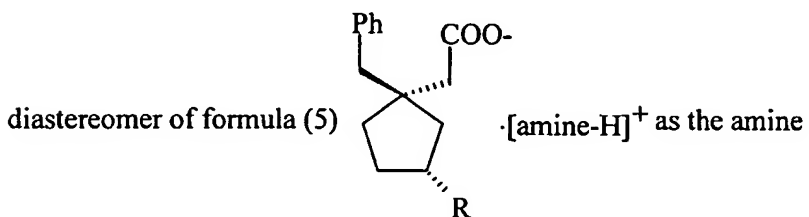


adding the products of Step b) above to an acid mixture and stirring



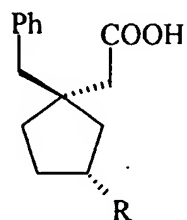
- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched

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salt; and

- e) converting the product of Step d) to a carboxylic acid of formula (6)

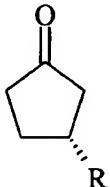


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19. A process according to Claim 18 which comprises:

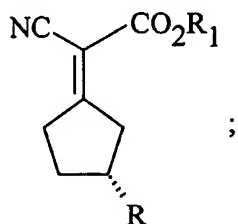
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$ wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl to a mixture of a chiral

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cyclopentanone of formula (1) , a solvent selected from

tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous sodium sulfate, anhydrous sodium carbonate, anhydrous potassium carbonate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate to produce the alkene of formula (2)

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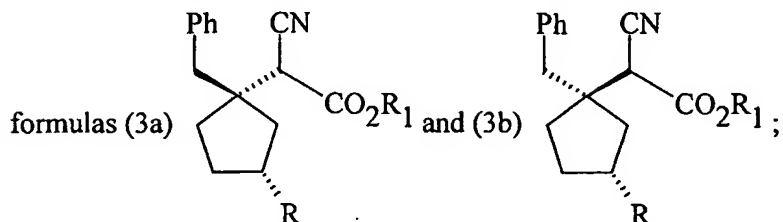


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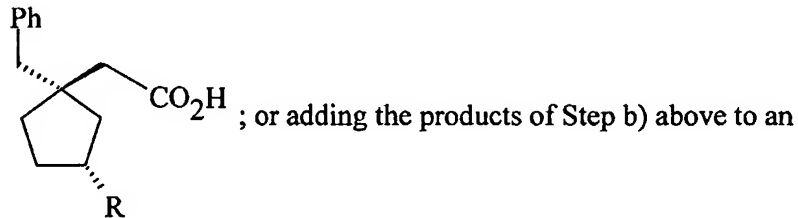
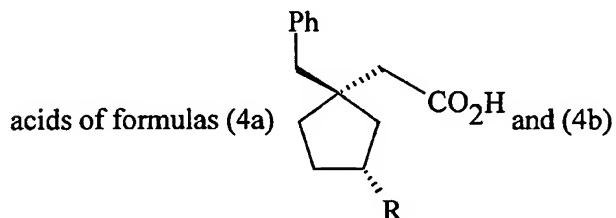
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, benzene, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and

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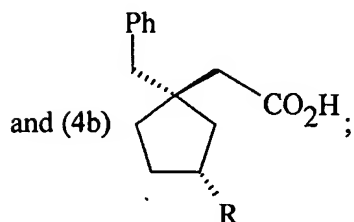
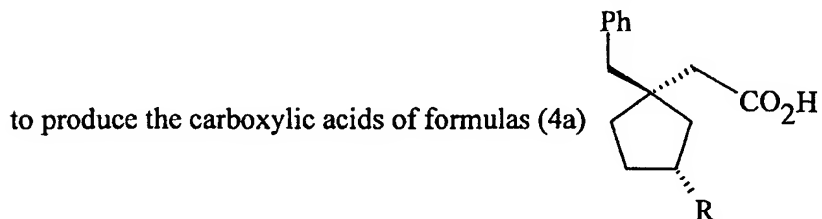
tert-butyl methyl ether to produce the addition products of



- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and stirring the mixture, and then acidifying to produce the carboxylic

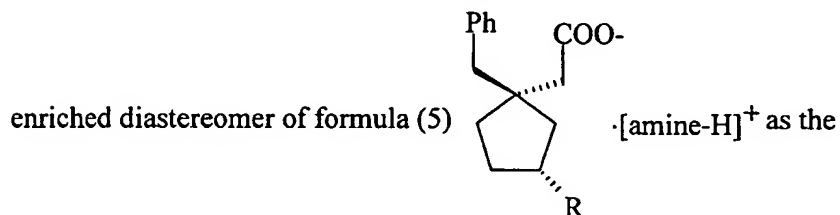


acid mixture selected from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid, and HBr in aqueous acetic acid, and stirring



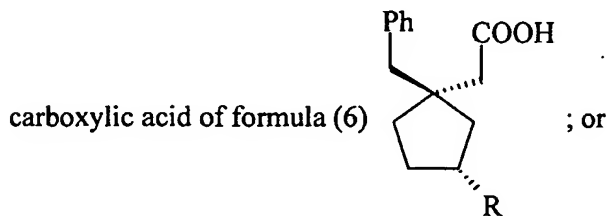
-192-

- d) contacting the products of Step c) above with an amine selected from (S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, benzene, xylenes, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile, *tert*-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the



amine salt; and

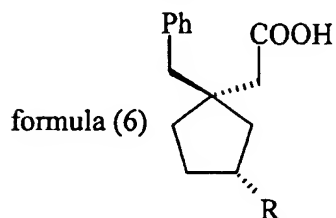
- e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the



partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and

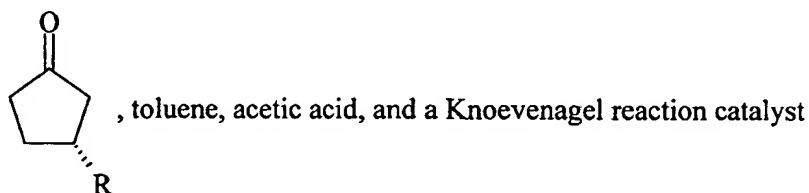
-193-

evaporating the organic layer to produce the carboxylic acid of

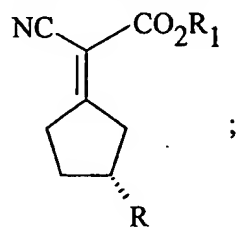


20. A process according to Claim 18 which comprises:

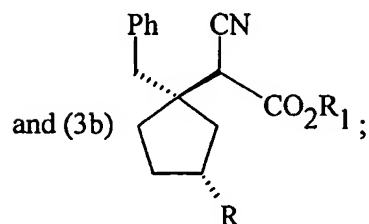
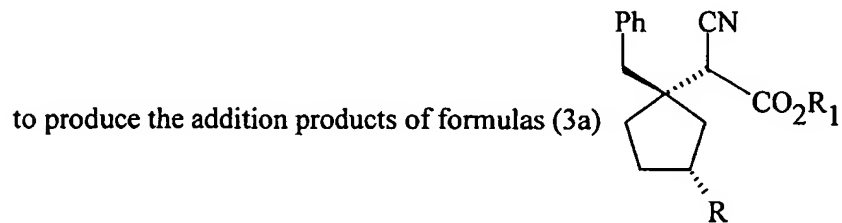
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (1)



which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (2)

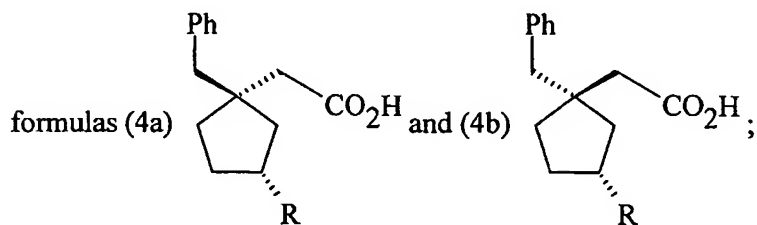


- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to 25°C

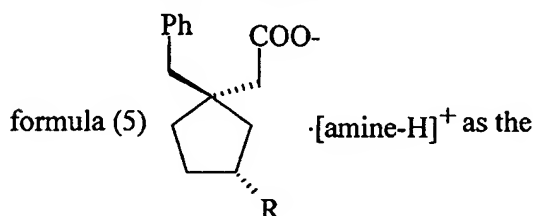


-194-

- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C, and then acidifying to produce the hydrolysis products of

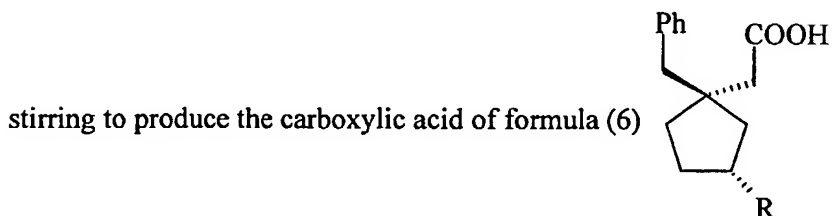


- 5 d) contacting the products of Step c) above with (S)- α -methylbenzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of

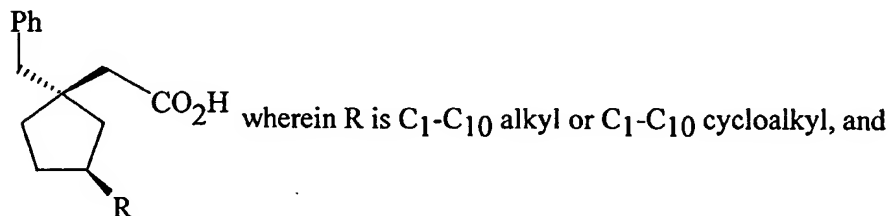


(S)- α -methylbenzylamine salt;

- 10 e) adding the product of Step d) to aqueous hydrochloric acid and



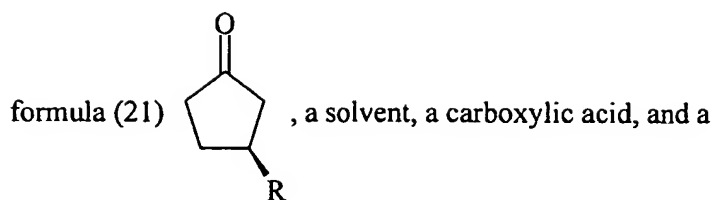
21. A process for the preparation of a compound of formula (26)



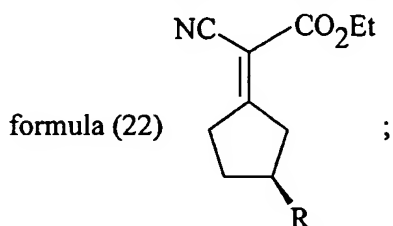
pharmaceutically acceptable salts thereof, which comprises:

- 15 a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R₁ is alkyl or benzyl, to a mixture of a chiral cyclopentanone of

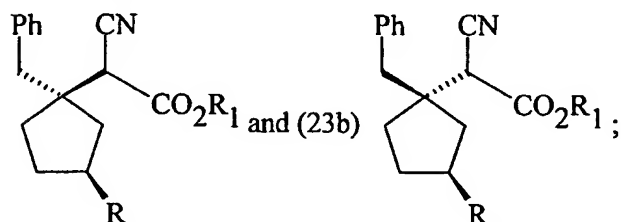
-195-



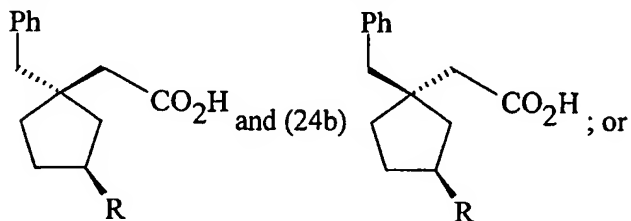
Knoevenagel reaction catalyst, and stirring the mixture in the presence of a means of removing water to produce the alkene of



- 5 b) adding the product of Step a) above to a mixture of benzylmagnesium chloride or benzylmagnesium iodide, in a solvent to produce the addition of products of formulas (23a)

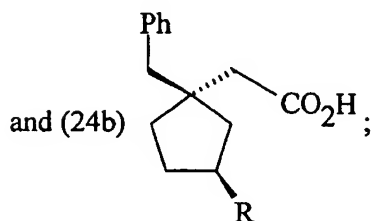
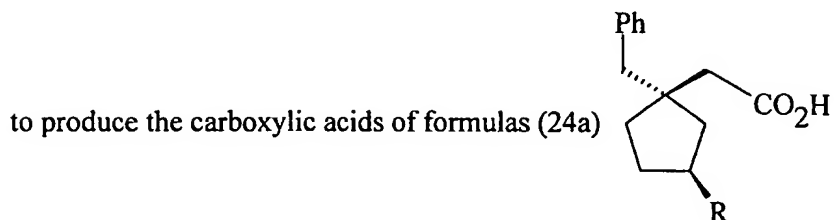


- 10 c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide, and a solvent, and stirring, and then acidifying to produce the carboxylic acids of formulas (24a)

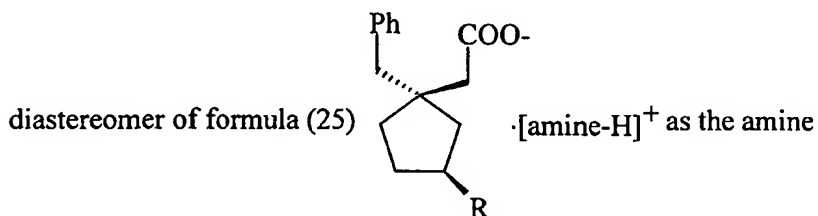


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adding the products of Step b) above to an acid mixture, and stirring

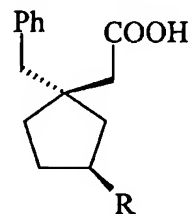


- d) contacting the products of Step c) above with an amine in a solvent, and recrystallizing the salt so formed to produce the enriched



salt; and

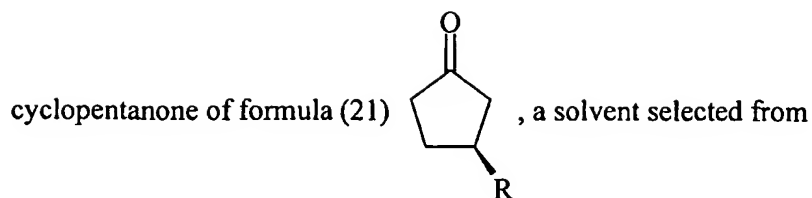
- e) converting the product of Step d) to a carboxylic acid of formula (26)



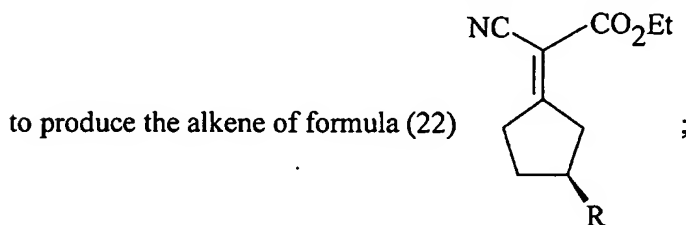
- 10 22. A process according to Claim 21 which comprises:

- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R_1 is selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, and benzyl, to a mixture of a chiral

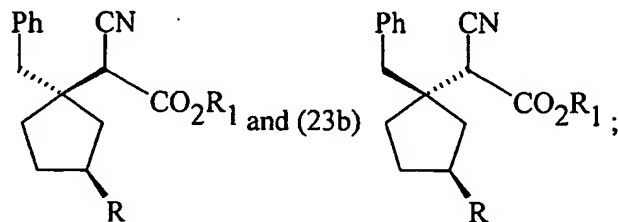
-197-



tetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, chloroform, dichloromethane, acetonitrile, ethyl ether, ethyl acetate, hexanes, N,N-dimethylformamide, dimethylsulfoxide, ethanol, *tert*-butanol, toluene, benzene, xylenes, and *n*-heptane, acetic acid, and a Knoevenagel reaction catalyst selected from β -alanine, ammonium acetate, and piperidine, and stirring the mixture in the presence of a means of removing water selected from azeotropic distillation, activated molecular sieves, anhydrous magnesium sulfate, anhydrous cesium carbonate, trimethyl orthoformate, and triethyl orthoformate



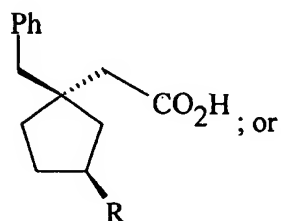
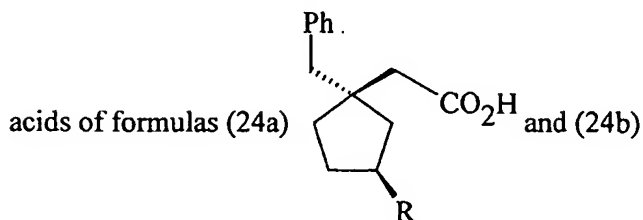
- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride, benzylmagnesium bromide, or benzylmagnesium iodide in a solvent selected from tetrahydrofuran, 1,4-dioxane, hexanes, *n*-heptane, toluene, diethyl ether, and *tert*-butyl methyl ether to produce the addition products of formulas (23a)



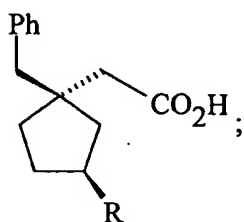
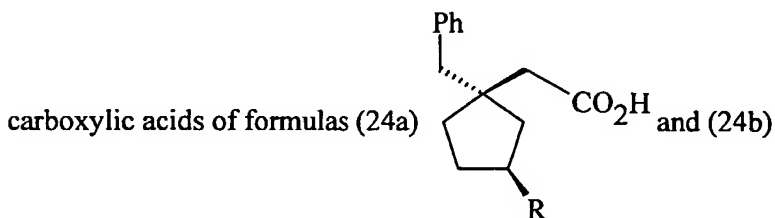
- c) adding the products of Step b) above to a mixture of a base selected from potassium hydroxide, sodium hydroxide, lithium hydroxide, and cesium hydroxide in a solvent selected from ethylene glycol, 2-methoxyethyl ether, 1,4-dioxane, and diethylene glycol, and

-198-

stirring the mixture, and then acidifying to produce the carboxylic



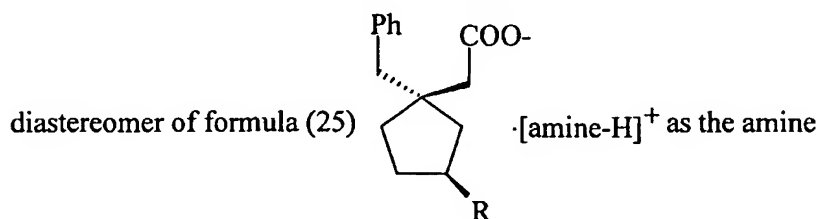
adding the products of Step b) above to an acid mixture selected
from 6-12 M HCl, 12 M H₂SO₄, 10%-48% wt/wt hydrobromic acid,
and HBr in aqueous acetic acid, and stirring to produce the



- d) contacting the products of Step c) above with an amine selected from
(S)- α -methyl-benzylamine, (R)- α -methyl-benzylamine, (R)-(+)-1-(naphthyl)ethylamine, (S)-(+)-1-(naphthyl)ethylamine, triethylamine, diisopropylethylamine, dicyclohexylamine, benzylamine, dibenzylamine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, and pyridine in a solvent selected from N,N-dimethylformamide, chloroform, hexanes, acetone, ethanol, methanol, *iso*-propanol, diethyl ether, dichloromethane, benzene, toluene, n-pentane, n-hexane, n-heptane, ethyl acetate, acetonitrile,

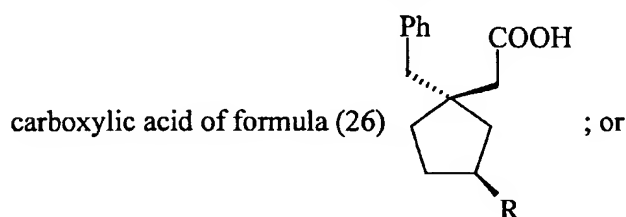
-199-

tert-butyl methyl ether, tetrahydrofuran, and 1,4-dioxane, and recrystallizing the salt so formed to produce the enriched

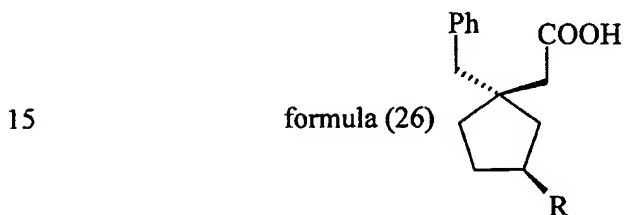


salt; and

- 5 e) adding the product of Step d) to a mixture selected from aqueous hydrochloric acid, aqueous sulfuric acid, aqueous acetic acid, hydrochloric acid dissolved in acetic acid, and hydrochloric acid dissolved in acetic acid and water, and stirring to produce the



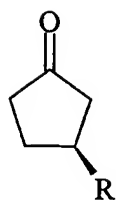
- 10 partitioning the product of Step d) between a mixture of aqueous hydrochloric acid and a solvent selected from chloroform, dichloromethane, ethyl acetate, ethyl ether, tetrahydrofuran, 1,4-dioxane, toluene, and *tert*-butylmethylether, and drying and evaporating the organic layer to produce the carboxylic acid of



23. A process according to Claim 21 which comprises:

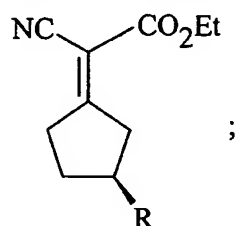
- a) adding a cyanoacetate of formula (A) $\text{NC}-\text{CH}_2-\text{CO}_2\text{R}_1$, wherein R_1 is ethyl, to a mixture of a chiral cyclopentanone of formula (21)

-200-



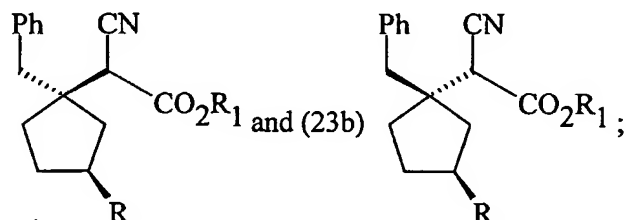
, toluene, acetic acid, and a Knoevenagel reaction catalyst

which is ammonium acetate, and heating the mixture at reflux over a Dean-Stark trap to produce the alkene of formula (22)



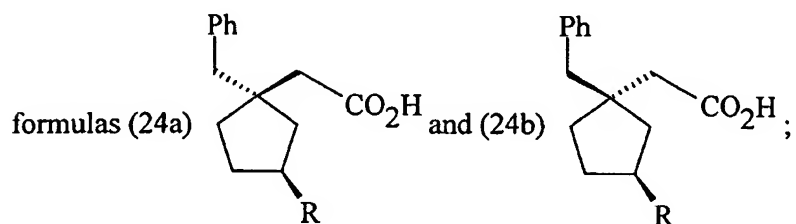
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- b) adding the product of Step a) above to a mixture of benzylmagnesium chloride in dry tetrahydrofuran at -100°C to -20°C to produce the addition products of formulas (23a)



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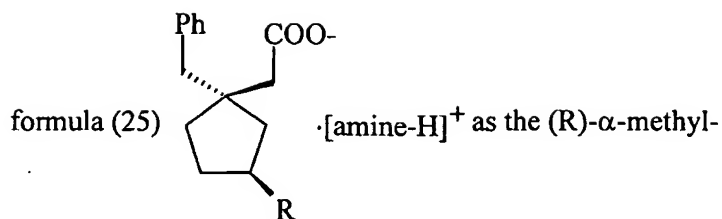
- c) adding the products of Step b) above to a mixture of potassium hydroxide in ethylene glycol, and heating the mixture at 100°C to 200°C , and then acidifying to produce the hydrolysis products of



- d) contacting the products of Step c) above with (R)- α -methylbenzylamine in ethyl acetate, and recrystallizing the salt so formed from ethyl acetate to produce the enriched diastereomer of

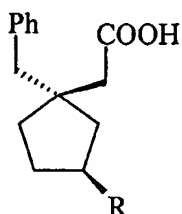
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-201-

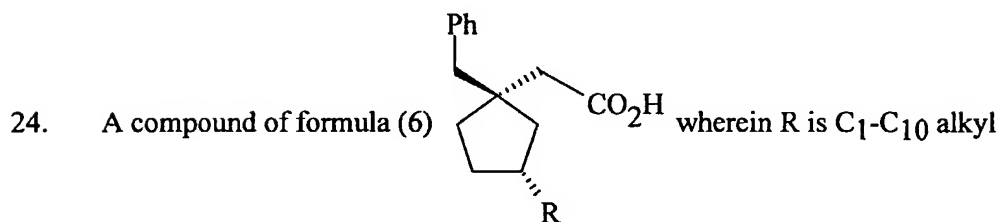


benzylamine salt; and

- e) adding the product of Step d) to aqueous hydrochloric acid and stirring to produce the carboxylic acid of formula (26)



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or C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof.

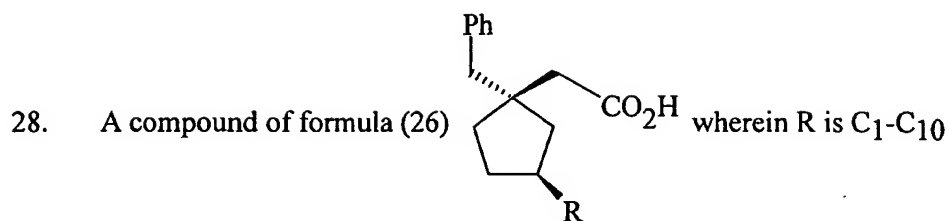
25. A compound according to Claim 24 wherein R is C₁-C₁₀ alkyl.

26. A compound according to Claim 24 wherein R is selected from methyl, ethyl, and *n*-propyl.

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27. A compound according to Claim 24 named ((1S,3R)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

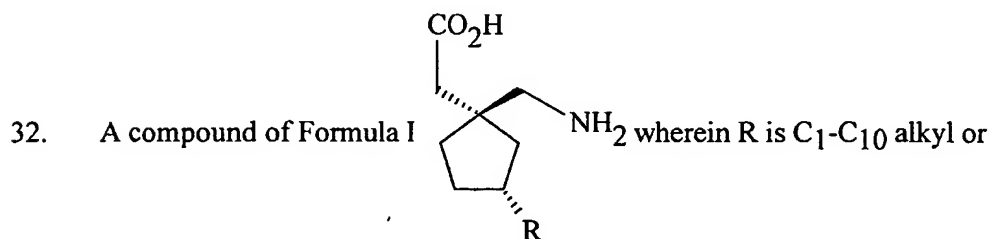
-202-

alkyl or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof.

29. A compound according to Claim 28 wherein R is C₁-C₁₀ alkyl.

30. A compound according to Claim 28 wherein R is selected from methyl, ethyl, and *n*-propyl.

31. A compound according to Claim 28 named ((1*R*,3*S*)-1-benzyl-3-methyl-cyclopentyl)-acetic acid.

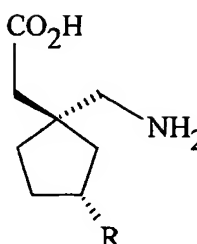


C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 1.

33. A compound according to Claim 32 wherein R is selected from methyl, ethyl, and *n*-propyl.

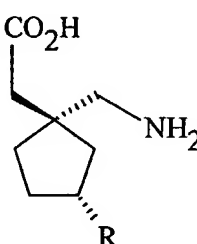
34. A compound according to Claim 32 selected from ((1*R*,3*R*)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid and ((1*R*,3*R*)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride.

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35. A compound of Formula II
- 
- wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 5.

36. A compound according to Claim 35 wherein R is selected from methyl, ethyl, and *n*-propyl.

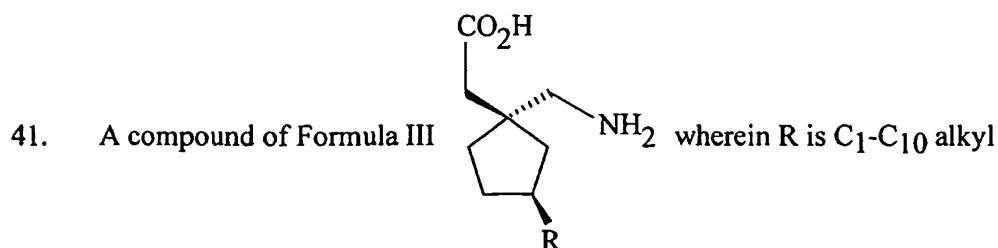
37. A compound according to Claim 35 selected from ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid and ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride.

38. A compound of Formula II
- 
- wherein R is C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 9.

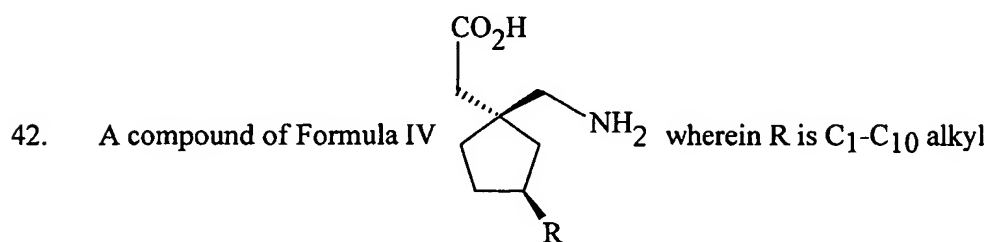
39. A compound according to Claim 38 wherein R is selected from methyl, ethyl, and *n*-propyl.

40. A compound according to Claim 38 selected from ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid and ((1S,3R)-1-aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride.

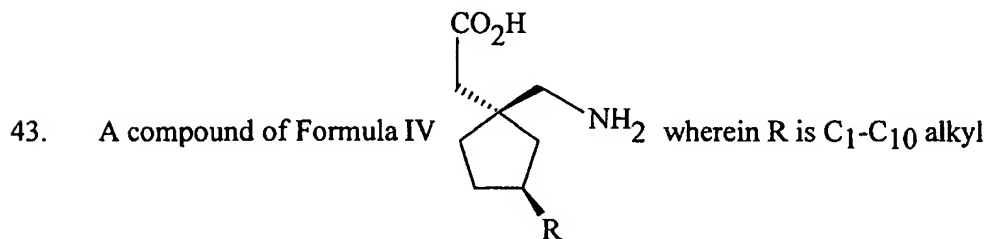
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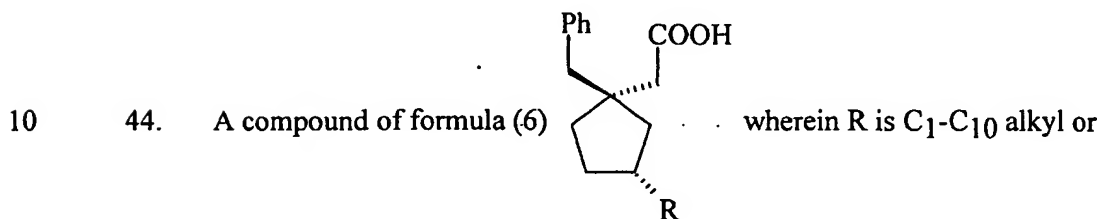
or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof,
prepared according to the process of Claim 15.



5 or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof,
prepared according to the process of Claim 16.

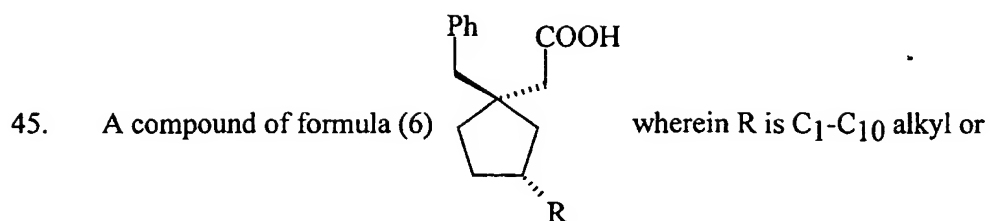


or C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof,
prepared according to the process of Claim 17.

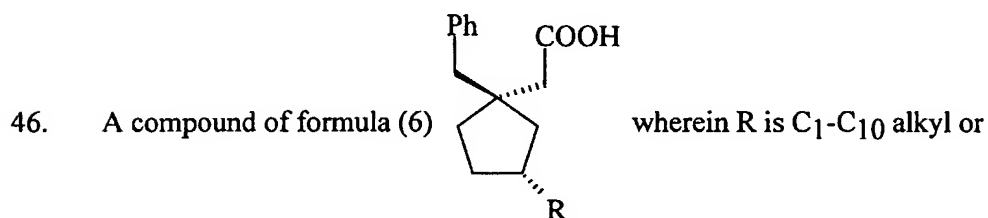


C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared
according to the process of Claim 18.

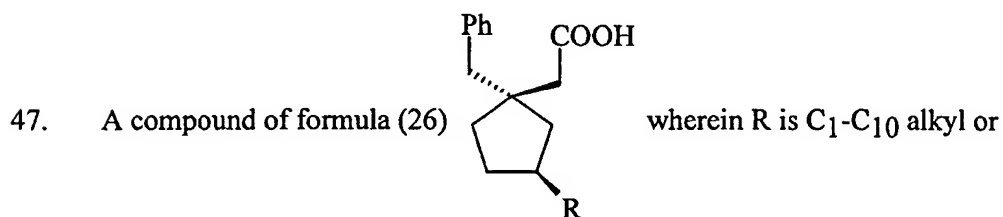
-205-



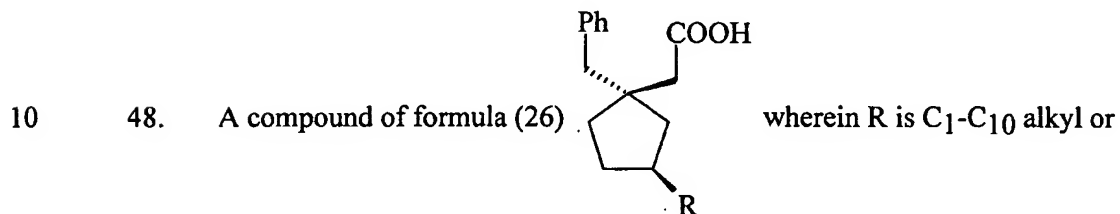
C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 19.



5 C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 20.

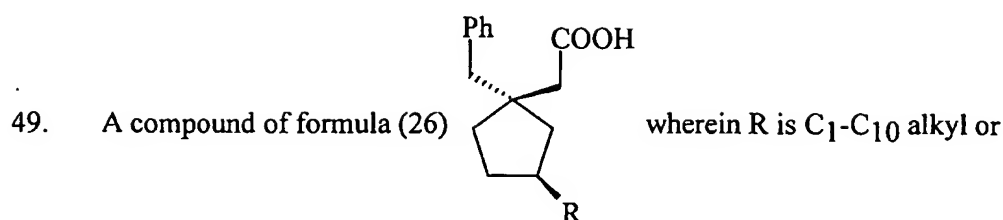


C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 21.



C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 22.

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C₃-C₁₀ cycloalkyl and pharmaceutically acceptable salts thereof, prepared according to the process of Claim 23.

50. A compound selected from:

- 5 E-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;
 Z-Cyano-((R)-3-methyl-cyclopentylidene)-acetic acid ethyl ester;
 (R)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid
 ethyl ester;
 (S)-((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid
 10 ethyl ester;
 (R)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid
 ethyl ester;
 (S)-((1R,3R)-1-Benzyl-3-methyl-cyclopentyl)-cyano-acetic acid
 ethyl ester;
 15 ((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentylmethyl)-
 benzene;
 ((1S,3R)-1-Benzyl-3-methyl-cyclopentylmethyl)-carbamic acid
 methyl ester;
 [(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-
 20 cyclopentyl]-acetic acid;
 ((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid methyl ester;
 (1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic
 acid;
 ((1R,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid
 25 methyl ester;
 [(1R,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-
 cyclopentyl]-acetic acid methyl ester;

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((1S,3R)-1-Benzyl-3-methyl-cyclopentyl)-acetic acid *tert*-butyl ester;

[(1S,3R)-1-Carboxymethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

5 [(1S,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl]-acetic acid *tert*-butyl ester;

 ((1R,3R)-1-Methoxycarbonylmethyl-3-methyl-cyclopentyl)-acetic acid;

 ((1S,3R)-1-Isocyanatomethyl-3-methyl-cyclopentyl)-acetic acid methyl ester; and

10 [(1S,3R)-1-(Methoxycarbonylamino-methyl)-3-methyl-cyclopentyl]-acetic acid methyl ester.

51. A compound selected from:

 ((1R,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

15 ((1R,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

 ((1R,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

 ((1R,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;

20 ((1R,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

 ((1R,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

52. A compound selected from:

 ((1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid;

25 ((1S,3R)-1-Aminomethyl-3-methyl-cyclopentyl)-acetic acid hydrochloride;

 ((1S,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid;

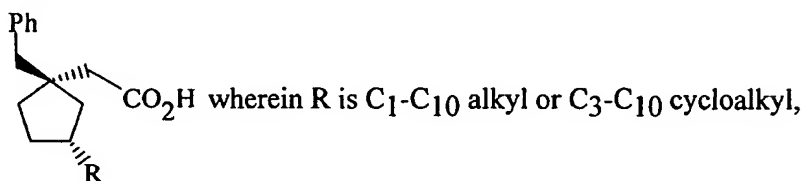
 ((1S,3R)-1-Aminomethyl-3-ethyl-cyclopentyl)-acetic acid hydrochloride;

30 ((1S,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid; and

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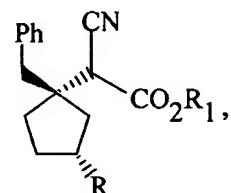
((1S,3R)-1-Aminomethyl-3-propyl-cyclopentyl)-acetic acid hydrochloride.

53. A process for the preparation of a compound of formula (4a)



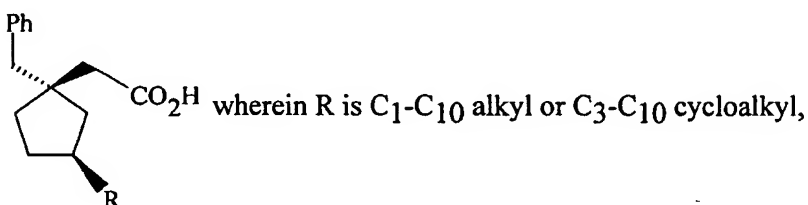
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comprising, hydrolyzing a compound of formula (3a)

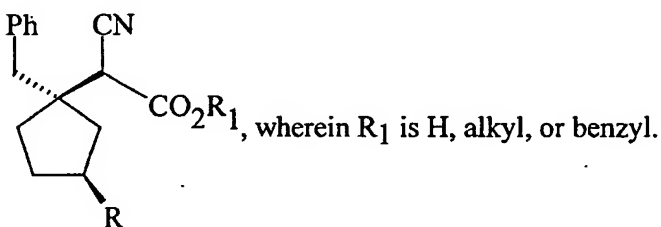


wherein R₁ is H, alkyl, or benzyl.

54. A process for the preparation of a compound of formula (24a)

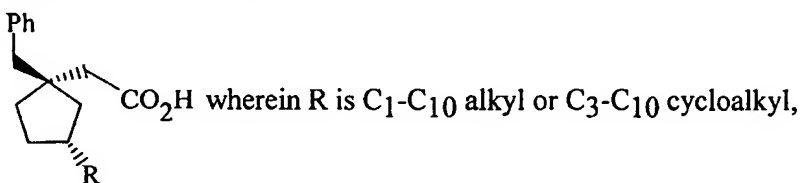


comprising, hydrolyzing a compound of formula (23a)



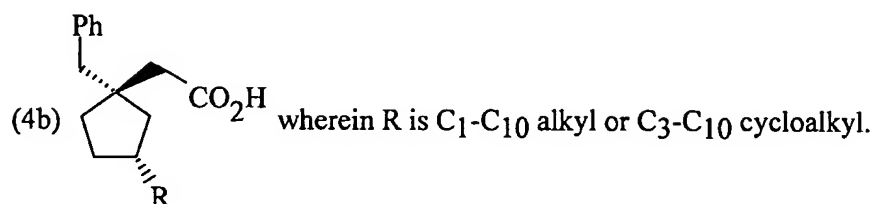
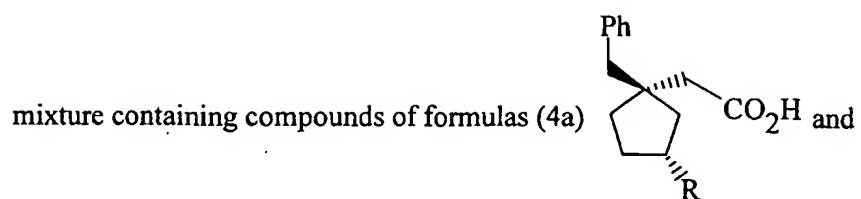
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55. A process for the preparation of a compound of formula (6)

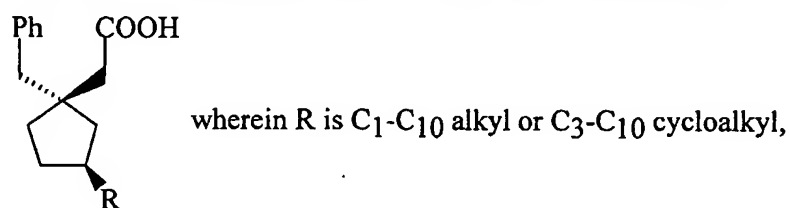


comprising, resolving a

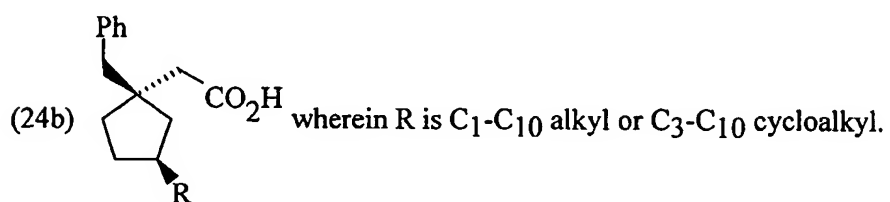
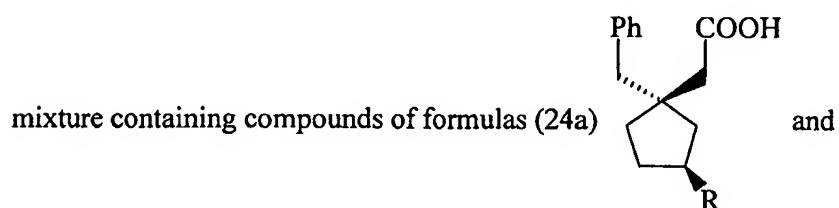
-209-



56. A process for the preparation of a compound of formula (26)

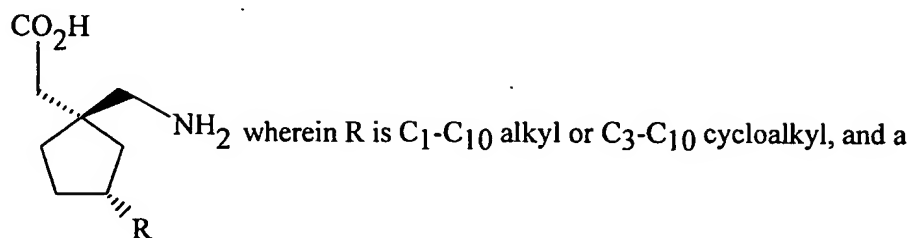


5 comprising, resolving a

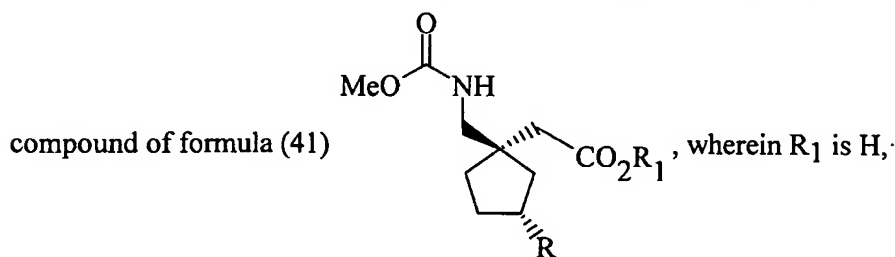


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57. A process for the preparation of a compound of Formula I

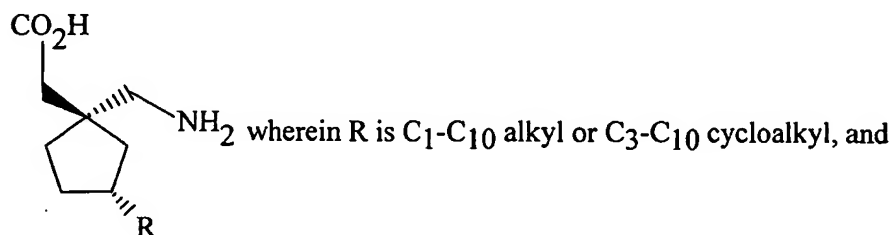


pharmaceutically acceptable salts thereof, comprising, hydrolyzing a

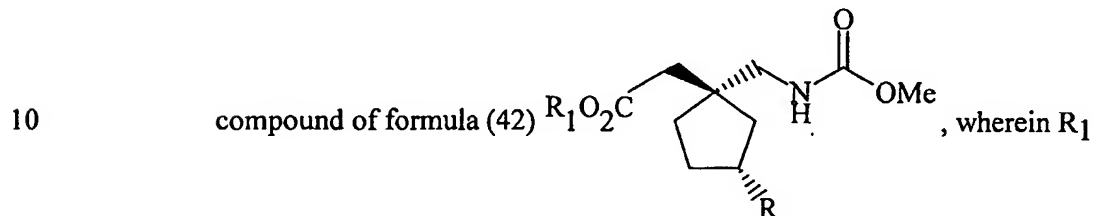


- 5 alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

58. A process for the preparation of a compound of Formula II



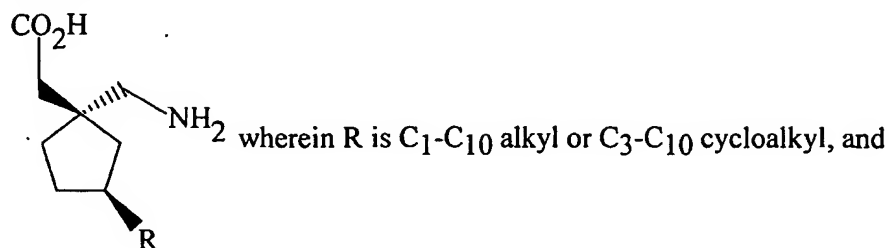
a pharmaceutically acceptable salts thereof, comprising, hydrolyzing a



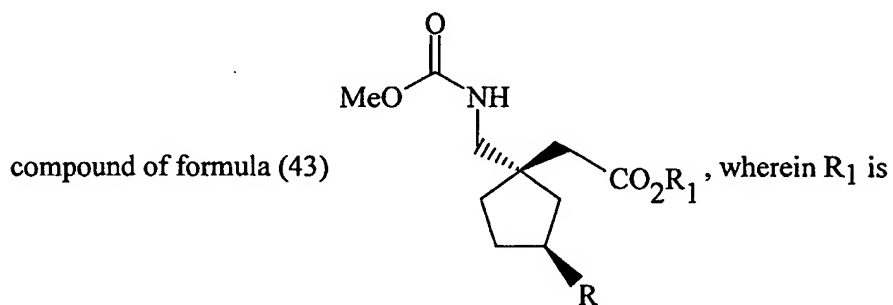
is H, alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

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59. A process for the preparation of a compound of Formula III

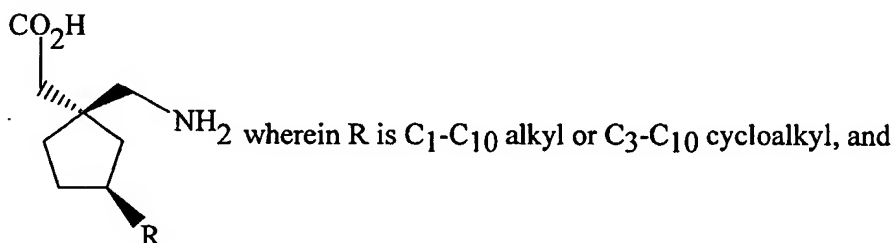


pharmaceutically acceptable salts thereof, comprising, hydrolyzing a

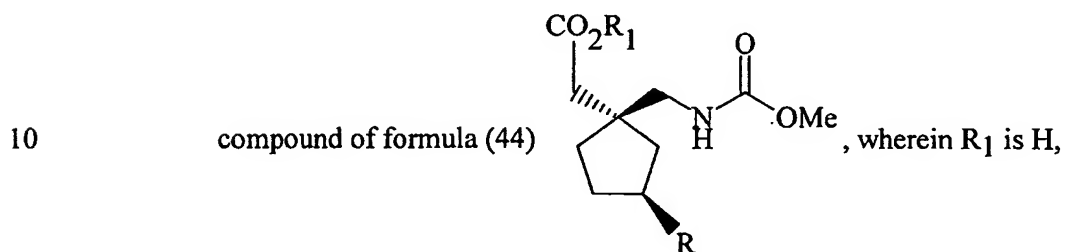


- 5 H, alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

60. A process for the preparation of a compound of Formula IV



pharmaceutically acceptable salts thereof, comprising, hydrolyzing a



alkyl, or benzyl, and contacting the product, if desired, with an acid or a base.

INTERNATIONAL SEARCH REPORT

 Intern I Application No
 PCT/US 00/32570

A. CLASSIFICATION OF SUBJECT MATTER

 IPC 7 C07C227/32 C07C229/28 C07C57/46 C07C255/31 C07C255/41
 C07C265/08 C07C271/12 C07C69/616

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WERNER HERZ: "Azulenes. VII. A Novel Rearrangement in the Synthesis of Azulenes" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 78, no. 7, 5 April 1956 (1956-04-05), pages 1485-1494, XP002161288 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 1493, column 2, line 57 -page 1494, column 1, line 26 --- -/--	1,5,9, 15-18, 21,50

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

23 February 2001

Date of mailing of the international search report

16/03/2001

Name and mailing address of the ISA

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Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/US 00/32570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 21824 A (WARNER-LAMBERT) 6 May 1999 (1999-05-06) page 4, line 12 - line 21; page 6, line 1 - line 10; table 1; examples 3,9	32-43, 51,52
A	claims -----	1,5,9, 15-18, 21,24, 28, 44-50, 53-60

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/32570

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921824 A	06-05-1999	AU 9663898 A	17-05-1999
		BR 9813284 A	22-08-2000
		CN 1276784 T	13-12-2000
		EP 1032555 A	06-09-2000
		NO 20002118 A	26-04-2000
		ZA 9809740 A	25-04-1999
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